Current Chemistry Letters 14 (2025) 51–58

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Design, synthesis, characterization and antimicrobial screening of newly synthesized indazoles of vanillin analogues

Krushnakumar L. Karangiya[a*], Manoj F. Dhaduk[a] and Jatin J. Upadhyay[b]

[a]*Bahauddin Government Science College, College Road, Junagadh, Gujrat, India*
[b]*M V M Science and Home Science College, Rajkot, Gujarat, India*

C H R O N I C L E

Article history:
Received July 18, 2024
Received in revised form
August 15, 2024
Accepted October 7, 2024
Available online
October 7, 2024

Keywords:
Heterocycles
Cyclohexanones
Indazoles
Chalcones
Vanillin
Anti-Microbial Activity

A B S T R A C T

A series of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-one derivatives **(3a-3i)** have been synthesized by refluxing of previously synthesized Ethyl-4-(aryl)-6-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates **(2a-2i)** with hydrazine hydrate in methanol for 7-8 hours in presence of catalytic amount of glacial acetic acid. The analytical and physical data of all the synthesized compounds **(2a-2i)** and **(3a-3i)** were observed and reported. The structures of each newly synthesized Indazole derivative have been characterized by various methods like Elemental analysis, Infrared spectroscopy, ^{1}H-NMR and ^{13}CMR spectroscopy and Mass spectroscopy. Furthermore, each compound was screened for its **in-vitro** antibacterial activity towards **Gram-positive** and **Gram-negative** bacterial strains and antifungal towards fungi **Aspergillus niger (A. niger)** and **Candida albicans (C. albicans)** with the concentration of 40 µg/ml and data was collected.

1. Introduction

The nitrogen bearing heterocycles are important class of heterocyclic compounds[1-7]. Overall, Indazoles are one of the most important classes of heterocyclic compounds having a bicyclic ring structure having fusion of pyrazole ring and a benzene ring with chemical formula $C_7H_6N_2$. It is common building blocks for many bioactive natural products and available drugs in the drug market. Due to pharmacologically important scaffolds, Indazole derivatives have considerable attention for drug researcher[8]. In nature many compounds having Indazole moiety, but this particular nucleus in a variety of synthetic compounds possesses many pharmacological activities, such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV activities[9-14]. Well-known indazole derivative, Niraparib anticancer drug is used for the treatment of primary peritoneal, breast and prostate cancer and recurrent epithelial ovarian, fallopian tube[15].

Indazole derivatives are emerging as potent pharmacologically active compound in recent decades and potential usefulness of these compounds are identified in several biological conditions like inhibition of apoptosis[16], treatment of rheumatoid arthritis[17]. Indazole having various activity like anti-proliferative activity[18-19], treatment of hypertension[20], anti-psychotic activity[21], hypotensive activity[22], treatment of obesity[23], tumor cell cytotoxic assays[24], anti-hyperlipidemic activity[25], trichomonacidal activity[26], Analgesic and antipyretic activity[27], anti-inflammatory activity[28], antitubercular activity[29] and anticancer activity[30] to be noted. Some Indazole derivatives are antimycobacterial agents[31] also.

* Corresponding author
E-mail address drdmfk@gmail.com (K. L. Karangiya)

doi: 10.5267/j.ccl.2024.10.002

2. Results and Discussion

2.1 Chemistry and Spectral Discussion

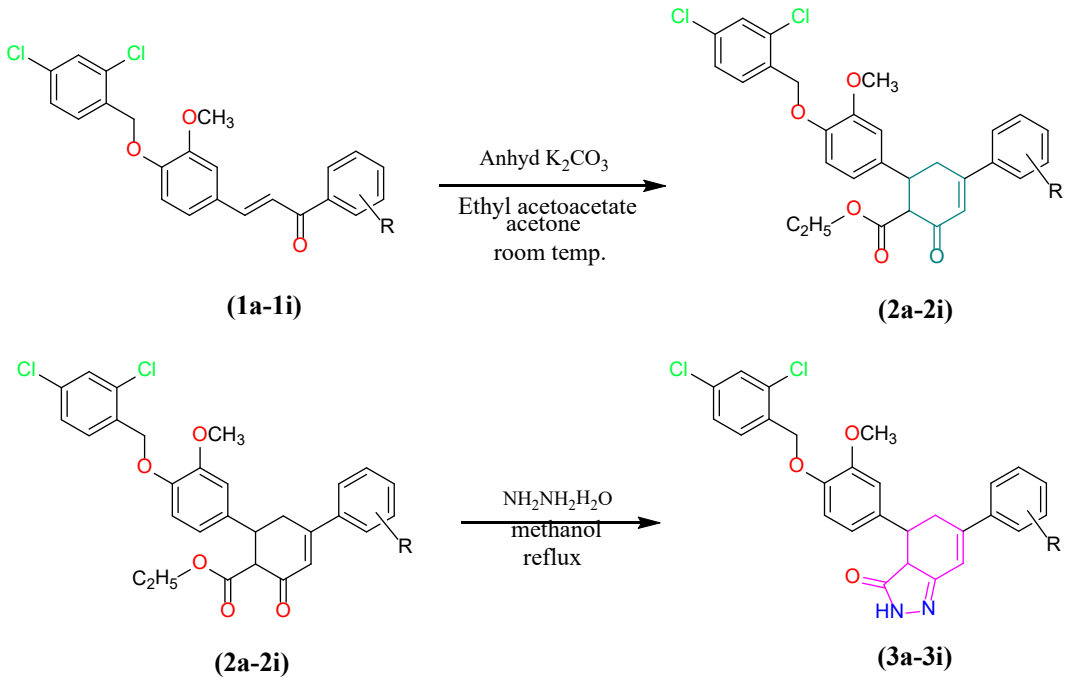
The targeted compounds 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydroindazol-3-ones **(3a-3i)** and Ethyl-4-(Aryl)-6-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates **(2a-2i)** were synthesized as charted in **scheme 1**. The purity of all compounds **(2a-2i)** and **(3a-3i)** is checked by thin layer chromatography and their characterization is carried out through elemental analysis, Infrared spectroscopy, ^{1}H-NMR and ^{13}CMR spectroscopy, and further supported by Mass spectroscopy. The physical and analytical data of compounds **(2a-2i)** and **(3a-3i)** were recorded.

Our main intention is to achieve the product with good yield, high purity and using green solvent for synthesis of compound **(3a-3i)**. We have carried out the experiments two different solvents i.e. methanol and ethanol. The observed data from the experiments is given in **Table 1.**

Table 1. Optimization reaction conditions for the synthesis of compound (3a-3i)

No.	Solvent	Time	Temperature	Yield
1	Methanol	7-8 hrs	reflux	55-80 %
2	Ethanol (95%)	10-12 hrs	reflux	40-60 %

When the reaction was carried out in Ethanol solvent at reflux temperature, the products obtained was much impure with less yield. Finally, we have chosen, methanol solvent with reflux temperature for synthesis of compound **(3a-3i)**. The FT−IR spectral data of synthesized Ethyl-4-(aryl)-6-[4-(2,4-dichlorobenzyloxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate derivatives show a strong band at 1649-1658 cm^{-1} for $\upsilon_{(C=O)}$ of cyclohexin-3-one ring and 1764-1794 cm^{-1} for $\upsilon_{(C=O)}$ of ethyl ester which is the characteristic band for cyclohexine-3-one. Insertion of nitrogen in the Indazole ring was characterized by appearance of band in range 3440-3457 cm^{-1} due to stretching of (N-H) group of Indazole. The ^{1}H-NMR also support the Ethyl-4-(aryl)-6-[4-(2,4-dichlorobenzyloxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate moiety by chemical shift at 2.96-3.59 δ for protons with three doublets of doublet for the cyclohexi-3-one ring protons. The signal in range 0.94-1.02 δ and 3.89-4.01 δ for 3H triplet and 2H quartet support to ethoxy (-OCH_2CH_3) group attach to cyclohexi-3-one ring. The one proton in range 6.59-7.54 δ for -NH- confirms the presence of secondary amine in indazole moiety. The molecular ion peak (m/z) is equivalent to their molecular weight of proposed compounds and the fragmentation pattern of synthesized indazole moiety matched with the typical fragmentation pattern of the indazole moiety that further confirming the structures of the compounds. The base peak at 159 (M+) in each synthesized compound support to synthesized compound and elemental analysis (% of C, H and N) data were found equivalent to their calculated value.



(1a-1i) **(2a-2i)** **(2a-2i)** **(3a-3i)**

R = -H, 4-Br, 4-Cl, 2-Cl, 2,4-Cl, 4-OH, 3-OH, 4-OCH_3, 2-NO_2

Scheme 1. Synthesis of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3a-3i)**

2.2 biological activity

All the synthesized compounds have been evaluated for antimicrobial activity.

Antibacterial activity

All the synthesized Indazoles derivatives (**3a-3i**) were screened for their antibacterial activity using the cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hours old subcultures of *Gram-positive* bacteria *Staphylococcus aureus (S. aureus)* and *Bacillus subtilis (B. subtilis)*, *Gram-negative* bacteria *Pseudomonas aeruginosa (P. aeruginosa)* and *Escherichia coli (E. coli)* in separate conical flasks at 40-50 ºC and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spread in a Petri dish (13 cm diameter) and allowed to set for 2 hours. The cups (10 mm diameter) were formed with the help of a borer in agar medium and filled with 0.04ml (40 µg) solution of the sample in DMF. The plates were incubated at 37 ºC for 24 hours and the control was also maintained with 0.04 ml of DMF similarly and the zone of inhibition of the bacterial growth was measured in *millimeters* and recorded in **Table 2**.

Antifungal activity

Aspergillus niger (A niger) and *Candida albicans (C albicans)* were employed for testing antifungal activity using the cup-plate method. The culture was maintained on *subouraud's agar slants*. Sterilized *sabouraud's agar* medium was inoculated for 72 hours and an old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of inoculated medium was evenly spread in a Petri dish and allowed to be set for two hours. The plates were incubated at 30 ˚C for 48 hours. After the completion of the incubation period, the zone of inhibition of growth in the form of diameter in *millimeters* was measured and recorded in **Table 2**. The collected data were compared with the standard drugs Fluconazole (an antifungal drug).

Table 2. Antimicrobial Screening Data of Compound ***(3a-3i)***

Code	R	Molecular Formula	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
			S. aureus		*P. aeruginosa*	*E. coli*	*A. niger*	
3a	C_6H_5-	$C_{27}H_{22}Cl_2N_2O_3$	10	13	11	09	13	11
3b	4-Br-C_6H_4-	$C_{27}H_{21}Cl_2BrN_2O_3$	17	**20**	**18**	**17**	06	10
3c	4-Cl-C_6H_4-	$C_{27}H_{21}Cl_3N_2O_3$	16	**19**	**20**	15	16	14
3d	2-Cl-C_6H_4-	$C_{27}H_{21}Cl_3N_2O_3$	13	16	**16**	14	07	04
3e	2,4-Cl_2-C_6H_3-	$C_{27}H_{20}Cl_4N_2O_3$	16	14	**16**	14	17	09
3f	4-OH-C_6H_4-	$C_{27}H_{22}Cl_2N_2O_4$	09	11	13	08	11	13
3g	2-OH-C_6H_4-	$C_{27}H_{22}Cl_2N_2O_4$	12	11	11	15	09	16
3h	4-OCH_3-C_6H_4-	$C_{28}H_{24}Cl_2N_2O_4$	15	07	12	10	12	05
3i	2-NO_2-C_6H_4-	$C_{27}H_{21}Cl_2N_3O_5$	11	08	06	14	10	12
	Sparfloxacin		**24**	**25**	**25**	**22**	-	-
	Benzylpenicillin		**18**	**17**	**16**	**16**	-	-
	Fluconazole		-	-	-	-	**22**	**20**

The antimicrobial screening data of all the synthesized Indazole derivatives **(3a-3i)** are collected and recorded in **Table 2**. The data show that the compound **3b** and **3c** have good antibacterial activity against *B. subtilis* (Gram positive bacteria) compare to Benzyl penicillin. The compound **3b, 3c** and **3b** have good antibacterial activity against (Gram positive bacteria) *P. aeruginosa* and *E. Coli* (Gram positive bacteria) respectively compare to Benzyl penicillin. The compound **3b** and **3c** has moderate antibacterial activity against *S. aureus, B. subtilis* (Gram positive bacteria) and *E. Coli* compare to Benzyl penicillin. The compound **3d** and **3e** have moderate antibacterial activity against (Gram positive bacteria) *P. aeruginosa* compare to Benzyl penicillin.

3. Experimental

3.1 Materials and methods

All required chemicals and solvents were purchased from Merck, Finar, and Spectrochem. The progress of the reaction and purity of each compound was monitored by thin-layer chromatography with silica gel as the stationary phase and a mixture of ethyl acetate and hexane in 3:7 proportion as mobile phase. Visualization was achieved with UV light using a UV chamber. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 8400 FTIR instrument in a KBr disc, and only significant absorbance levels (cm^{-1}) are listed. ^{1}H-NMR spectra (400 MHz) were recorded on a "Bruker AVANCE III spectrometer" using different solvents with TMS as an internal standard, and chemical shifts were recorded in δ ppm. Mass spectra were determined using a direct inlet probe on a GCMS-QP2010 mass spectrometer (Shimadzu, Kyoto, Japan). Elemental analysis was performed on Carlo Erba EA1108 elemental analyzer.

3.2 General Procedure

*3.2.1 Procedure of synthesis of Ethyl-4-(aryl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates **(2a-2i)***

The mixture of *(E)*-1-Aryl-3-(4-((2,4-dichlorobenzyl) oxy)-3-methoxyphenyl) prop-2-en-1-ones (0.01 mole), anhydrous K_2CO_3 and ethyl acetoacetate (0.01 mole) in dry acetone (20 mL) was stirred at room temperature about 36 hours. The progress of the reaction was monitored by TLC (Thin-Layer Chromatography) using hexane-ethyl acetate (7:3) as an eluent and after competition of the reaction, the reaction mixture was filtered and kept it aside for three to four days till the solvent is evaporated. After evaporation of solvent the separated solid was collected and crystallized from ethanol to give desired product.

Similarly, a series of different Ethyl-4-(aryl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates **(2a-2i)** derivatives were synthesized. The analytical and physical data of all the synthesized compounds were recorded.

*3.2.2 Procedure of synthesis of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3a-3i)***

Mixture of Ethyl-4-(aryl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates (0.01 mole) **(2a-2i)** and hydrazine hydrate (0.01 mole) in methanol (10 mL) was refluxed for 7-8 hours in presence of few drops of glacial acetic acid as a catalyst. The progress of the reaction was monitored by TLC (Thin-Layer Chromatography) using hexane-ethyl acetate (3:7) as an eluent and after competition of the reaction, the reaction mixture was cooled and to pour into crushed ice. To collect the solid separated out and recrystallized it from ethanol. Similarly, a series of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3a-3i)** derivatives were synthesized. The physical and analytical data were recorded.

*3.3 Spectral and physical data of Ethyl-4-(aryl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoates **(2a-2i)***

*3.3.1 Ethyl-4-(phenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2a)***

Yield 56%; m.p. 127-129°C; IR (KBr) cm^{-1}: 2941(C-H str.), 3096 (Ar C-H str.), 1260 (Ar-O-C Str.), 1764 (C=O, Str. of ester), 1657 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 1.01 (t, 3H,-$OCH_2C\underline{H}_3$), 2.89 (1H, dd, -CH_d-), 3.12 (1H, dd, -CH_d-), 3.63 (1H, dd, -CH_e-), 3.77 (3H, s,-OCH_3), 3.89 (q, 2H, -$OC\underline{H}_2CH_3$), 4.12 (d, 1H, -CH_f-), 5.19 (s, 2H, -O-CH_2-), 6.51 (s, 1H, -CH_e-), 6.50-7.55 (11H, m, Ar-H); Mass (m/z): 524(M+). Elemental Analysis: $C_{29}H_{26}Cl_2O_5$; C, 66.22; H, 4.79%.

*3.3.2 Ethyl-4-(4-bromophenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2b)***

Yield 62%; m.p. 122-124°C; IR (KBr) cm^{-1}: 2976 (C-H Str.), 3072 (Ar C-H Str.), 1255 (Ar-O-C Str.), 1728 (C=O Str. of ester), 1649 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 0.96 (t, 3H,-$OCH_2C\underline{H}_3$), 2.96 (1H, dd, -CH_d-), 3.08 (1H, dd, -CH_d-), 3.60 (1H, dd, -CH_e-), 3.78 (3H, s,-OCH_3), 3.92 (q, 2H, -$OC\underline{H}_2CH_3$), 4.09 (d, 1H, -CH_f-), 5.10 (s, 2H, -O-CH_2-), 6.56 (s, 1H, -CH_e-), 6.90-7.68 (10H, m, Ar-H); Mass (m/z): 602(M+), 604(M+2); Elemental Analysis: $C_{29}H_{25}BrCl_2O_5$; C, 57.34; H, 4.18%.

*3.3.3 Ethyl-4-(4-chlorophenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2c)***
Yield 55%; m.p. 137-140°C; IR (KBr) cm^{-1}: 2933 (C-H Str.), 3022 (Ar C-H Str.), 1250 (Ar-O-C Str.), 1785 (C=O, Str. of ester), 1650 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 0.94 (t, 3H,-$OCH_2C\underline{H}_3$), 2.90 (1H, dd, -CH_d-), 3.10 (1H, dd, -CH_d-), 3.57 (1H, dd, -CH_e-), 3.70 (3H, s, -OCH_3), 3.89 (q, 2H, -$OC\underline{H}_2CH_3$), 4.12 (d, 1H, -CH_f-), 5.13 (s, 2H, -O-CH_2-), 6.50 (s, 1H, -CH_e-), 6.80-7.62 (10H, m, Ar-H); Mass (m/z): 560(M+), 562(M+2), 564(M+4); Elemental Analysis: $C_{29}H_{25}Cl_3O_5$; C, 62.24; H, 4.55%.

*3.3.4 Ethyl-4-(2-chlorophenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2d)***
Yield 67%; m.p. 122-123°C; IR (KBr) cm^{-1}: 2932 (C-H Str.), 3056 (Ar C-H Str.), 1263 (Ar-O-C Str.), 1758 (C=O, Str. of ester), 1661 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 0.93 (t, 3H, -$OCH_2C\underline{H}_3$), 2.91 (1H, dd, -CH_d-), 3.15 (1H, dd, -CH_d-), 3.50 (1H, dd, -CH_e-), 3.71 (3H, s, -OCH_3), 3.87 (q, 2H, -$OC\underline{H}_2CH_3$), 4.09 (d, 1H, -CH_f-), 5.11 (s, 2H, -O-CH_2-), 6.49 (s, 1H, -CH_e-), 6.92-7.68 (10H, m, Ar-H); Mass (m/z): 560(M+), 562(M+2); Elemental Analysis: $C_{29}H_{25}Cl_3O_5$; C, 62.27; H, 4.57%.

*3.3.5 Ethyl-4-(2,4-dichlorophenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2e)***

Yield 46%; m.p. 117-119°C; IR (KBr) cm^{-1}: 2942 (C-H Str.), 3025 (Ar C-H Str.), 1256 (Ar-O-C Str.), 1794 (C=O, Str. of ester), 1653 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 1.03 (t, 3H, -$OCH_2C\underline{H}_3$), 2.78 (1H, dd, -CH_d-), 3.111 (1H, dd, -CH_d-), 3.41 (1H, dd, -CH_c-), 3.69 (3H, s, -OCH_3), 3.81 (q, 2H, -$OC\underline{H}_2CH_3$), 3.99 (d, 1H, -CH_f-), 5.14 (s, 2H, -O-CH_2-), 6.58 (s, 1H, -CH_e-), 7.14-7.99 (9H, m, Ar-H); Mass (m/z): 594(M+), 596(M+2), 598(M+4); Elemental Analysis: $C_{29}H_{24}Cl_4O_5$; C, 58.56; H, 4.11%.

*3.3.6 Ethyl-4-(4-hydroxyphenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2f)***

Yield 77%; m.p. 135-136°C; IR (KBr) cm^{-1}: 2936 (C-H Str.), 3032 (Ar C-H Str.), 1255(Ar-O-C Str.), 1790 (C=O, Str. of ester), 1657 (C=O, Str. of ring), 3466 (Ar-OH Str.); ^{1}H-NMR ($CDCl_3$): 0.99 (t, 3H, -$OCH_2C\underline{H}_3$), 2.90 (1H, dd, -CH_d-), 3.11 (1H, dd, -CH_d-), 3.47 (1H, dd, -CH_c-), 3.73 (3H, s, -OCH_3), 3.81 (q, 2H, -$OC\underline{H}_2CH_3$), 4.02 (d, 1H, -CH_f-), 5.13 (s, 2H, -O-CH_2-), 5.25 (1H, s, -OH), 6.47 (s, 1H, -CH_e-), 6.82-7.70 (10H, m, Ar-H); Mass (m/z): 540(M+), 542(M+2); Elemental Analysis: $C_{29}H_{26}Cl_2O_6$; C, 64.22; H, 4.81%.

*3.3.7 Ethyl-4-(2-hydroxyphenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2g)***

Yield 67%; m.p. 145-147°C; IR (KBr) cm^{-1}: 2938 (C-H Str.), 3026 (Ar C-H Str.), 1254 (Ar-O-C Str.), 1791 (C=O, Str. of ester), 1645 (C=O, Str. of ring), 3472 (Ar-OH Str.); ^{1}H-NMR ($CDCl_3$): 0.97 (t, 3H, -$OCH_2C\underline{H}_3$), 2.93 (1H, dd, -CH_d-), 3.13 (1H, dd, -CH_d-), 3.48 (1H, dd, -CH_c-), 3.69 (3H, s, -OCH_3), 3.78 (q, 2H, -$OC\underline{H}_2CH_3$), 4.07 (d, 1H, -CH_f-), 5.09 (s, 2H, -O-CH_2-), 5.19 (1H, s, -OH), 6.41 (s, 1H, -CH_e-), 6.80-7.59 (10H, m, Ar-H); Mass (m/z): 540(M+), 542(M+2); Elemental Analysis: $C_{29}H_{26}Cl_2O_6$; C, 64.30; H, 4.84%.

*3.3.8 Ethyl-4-(4-methoxyphenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2h)***

Yield 78%; m.p. 183-185°C; IR (KBr) cm^{-1}: 2942 (C-H Str.), 3033 (Ar C-H Str.), 1252 (Ar-O-C Str.), 1794 (C=O, Str. of ester), 1652 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 1.03 (t, 3H,-$OCH_2C\underline{H}_3$), 2.90 (1H, dd, -CH_d-), 3.11 (1H, dd, -CH_d-), 3.43 (1H, dd, -CH_c-), 3.67 (3H, s, -OCH_3), 3.72 (q, 2H, -$OC\underline{H}_2CH_3$), 3.84 (3H, s, -OCH_3), 4.03 (d, 1H, -CH_f-), 5.10 (s, 2H, -O-CH_2-), 6.41 (s, 1H, -CH_e-), 6.80-7.59 (10H, m, Ar-H); Mass (m/z): 554(M+), 556(M+2); Elemental Analysis: $C_{30}H_{28}Cl_2O_6$; C, 64.82; H, 5.08%.

*3.3.9 Ethyl-4-(2-nitrophenyl)-6-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2-oxo-cyclohex-3-eneoate **(2i)***

Yield 66%; m.p. 201-203°C; IR (KBr) cm^{-1}: 2936 (C-H Str.), 3025 (Ar C-H Str.), 1253 (Ar-O-C Str.), 1792 (C=O, Str. of ester), 1656 (C=O, Str. of ring); ^{1}H-NMR ($CDCl_3$): 0.99 (t, 3H, -$OCH_2C\underline{H}_3$), 2.91 (1H, dd, -CH_d-), 3.10 (1H, dd, -CH_d-), 3.38 (1H, dd, -CH_c-), 3.61 (3H, s, -OCH_3), 3.69 (q, 2H, -$OC\underline{H}_2CH_3$), 4.03 (d, 1H, -CH_f-), 5.04 (s, 2H, -O-CH_2-), 6.46 (s, 1H, -CH_e-), 6.84-7.69 (10H, m, Ar-H); Mass (m/z): 569(M+), 571(M+2); Elemental Analysis: $C_{29}H_{25}Cl_2NO_7$; C, 60.89; H, 4.43; N, 2.43%.

*3.4 Physical and spectral data of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3a-3i)***

*3.4.1 6-(phenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3a)***

Yield 77%; m.p. 114-116°C; IR (KBr) cm^{-1}: 2982 (C-H Str.), 3038 (Ar C-H Str.), 1588 (C=N), 1260 (Ar-O-C Str.), 3440 (N-H, str. of cyclic amide), 1791 (C=O, str. of ring), 680 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.14 (1H, dd, -CH_d-), 3.30 (1H, dd, -CH_d-), 3.71 (1H, dd, -CH_e-), 3.75 (1H, s, -CH_c-), 3.88 (s, 3H, -OCH_3), 5.01 (s, 2H, -O-CH_2-), 5.11 (1H, d, -CH_f-), 6.41-7.39 (12H, m,-NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.44 (C=O), 156.14, 149.32, 148.09, 147.12, 141.78, 137.01, 134.44, 132.54, 130.48, 129.69, 128.68, 127.09, 126.41, 119.47, 112.21, 111.24, 109.86, 67.13 (-O-CH_2-), 56.11(-OCH_3), 52.15, 34.50 (-CH_2-) and 30.07 δ; Mass (m/z): 492(M+), 494(M+2); Elemental Analysis: $C_{27}H_{22}Cl_2N_2O_3$; C, 65.81; H, 4.51; N, 5.71%.

*3.4.2 6-(4-bromophenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3b)***

Yield 69%; m.p. 163-165°C; IR(KBr) cm^{-1}: 2980 (C-H Str.), 3012 (Ar C-H Str.), 1591 (C=N), 1263 (Ar-O-C Str.), 3444 (N-H, str. of cyclic amide), 1793 (C=O, str. of ring), 682 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.11 (1H, dd, -CH_d-), 3.34 (1H, dd, -CH_d-), 3.76 (1H, dd, -CH_e-), 3.77 (1H, s, -CH_c-), 3.83 (s, 3H, -OCH_3), 5.06 (s, 2H, -O-CH_2-), 5.09 (1H, d, -CH_f-), 6.59-7.52 (11H, m,-NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.43 (C=O), 155.68, 149.54, 148.08, 147.03, 141.57, 136.22, 134.53, 133.68, 132.46, 131.35, 130.46, 129.19, 126.10, 121.23, 119.47, 112.13, 111.21, 67.12 (-O-CH_2-), 56.10 (-OCH_3), 52.09, 34.25 (-CH_2-) and 30.08 δ; Mass (m/z): 570(M+), 572(M+2); Elemental Analysis: $C_{27}H_{21}Cl_2BrN_2O_3$; C, 56.72; H, 3.71; N, 4.92%.

3.4.3 6-(4-chlorophenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3c)***

Yield 56%; m.p. 182-185°C; IR(KBr) cm^{-1}: 2967 (C-H Str.), 3039 (Ar C-H Str.), 1578 (C=N), 1262 (Ar-O-C Str.), 3457 (N-H, str. of cyclic amide), 1797 (C=O, str. of ring), 685 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.13 (1H, dd, -CH_d-), 3.37 (1H, dd, -CH_d-), 3.74 (1H, dd, -CH_e-), 3.72 (1H, s, -CH_c-), 3.80 (s, 3H, -OCH_3), 5.07 (s, 2H, -O-CH_2-), 5.11 (1H, d, -CH_f-), 6.62-7.75 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.40 (C=O), 155.61, 149.50, 148.02, 146.93, 141.63, 135.32, 134.63, 133.98, 133.34, 132.49, 130.41, 129.79, 128.65, 127.13, 127.96, 119.47, 112.13, 111.21, 67.18 (-O-CH_2-), 56.06 (-OCH_3), 52.11, 34.36 (-CH_2-) and 30.06 δ; Mass (m/z): 526(M+), 528(M+2); Elemental Analysis: $C_{27}H_{21}Cl_3N_2O_3$; C, 61.55; H, 4.08; N, 5.33%.

3.4.4 6-(2-chlorophenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3d)***

Yield 67%; m.p. 153-154°C; IR(KBr) cm^{-1}: 2943 (C-H Str.), 3019 (Ar C-H Str.), 1591 (C=N), 1256 (Ar-O-C Str.), 3439 (N-H, str. of cyclic amide), 1799 (C=O, str. of ring), 681 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.12 (1H, dd, -CH_d-), 3.36 (1H, dd, -CH_d-), 3.85 (1H, dd, -CH_e-), 3.63 (1H, s, -CH_c-), 3.84 (s, 3H, -OCH_3), 5.02 (s, 2H, -O-CH_2-), 5.14 (1H, d, -CH_f-), 6.68-7.59 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.46 (C=O), 155.63, 149.54, 148.03, 146.91, 141.53, 135.12, 134.63, 133.78, 133.33, 132.49, 131.14, 130.41, 129.79, 129.21, 127.85, 127.13, 126.76, 119.47, 112.13, 111.21, 67.18 (-O-CH_2-), 56.09 (-OCH_3), 52.13, 34.31 (-CH_2-) and 30.09 δ; Mass (m/z): 526(M+), 528(M+2); Elemental Analysis: $C_{27}H_{21}Cl_3N_2O_3$; C, 61.42; H, 4.02; N, 5.36%.

3.4.5 6-(2,4-dichlorophenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3e)***

Yield 79%; m.p. 197-200°C; IR(KBr) cm^{-1}: 2949 (C-H Str.), 3009 (Ar C-H Str.), 1589 (C=N), 1259 (Ar-O-C Str.), 3443 (N-H, str. of cyclic amide), 1781 (C=O, str. of ring), 680 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.09 (1H, dd, -CH_d-), 3.24 (1H, dd, -CH_d-), 3.94 (1H, dd, -CH_e-), 3.57 (1H, s, -CH_c-), 3.80 (s, 3H, -OCH_3), 5.07 (s, 2H, -O-CH_2-), 5.17 (1H, d, -CH_f-), 6.58-7.92 (10H, m,-NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.40 (C=O), 155.63, 149.54, 148.03, 146.91, 141.53, 135.12, 134.63, 133.78, 133.33, 132.49, 131.14, 130.41, 129.21, 128.94, 127.13, 126.80, 125.21, 119.47, 112.13, 111.21, 67.08 (-O-CH_2-), 56.06 (-OCH_3), 52.10, 34.33 (-CH_2-) and 30.03 δ; Mass (m/z): 562(M+), 564(M+2); Elemental Analysis: $C_{27}H_{20}Cl_4N_2O_3$; C, 57.77; H, 3.62; N, 5.01%.

3.4.6 6-(4-hydroxyphenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3f)***

Yield 81%; m.p. 196-199°C; IR(KBr) cm^{-1}: 3514 (Ar-OH Str.), 2939 (C-H Str.), 3065 (Ar C-H Str.), 1599 (C=N), 1254 (Ar-O-C Str.), 3441 (N-H, str. of cyclic amide), 1791 (C=O, str. of ring), 685 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.07 (1H, dd, -CH_d-), 3.27 (1H, dd, -CH_d-), 3.65 (1H, dd,-CH_e-), 3.54 (1H, s, -CH_c-), 3.74 (s, 3H, -OCH_3), 5.09 (s, 2H, -O-CH_2-), 5.11 (1H, d, -CH_f-), 5.27 (1H, s, Ar-OH), 6.61-7.79 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.40 (C=O), 157.27, 155.16, 150.01, 148.09, 147.02, 142.71, 136.07, 134.54, 132.84, 130.18, 129.79, 127.08, 119.47, 115.85, 112.14, 111.24, 109.96, 67.15 (-O-CH_2-), 56.16 (-OCH_3), 52.13, 34.52 (-CH_2-) and 29.97 δ; Mass (m/z): 508(M+), 510(M+2); Elemental Analysis: $C_{27}H_{22}Cl_2N_2O_4$; C, 63.71; H, 4.37; N, 5.56%.

3.4.7 6-(2-hydroxyphenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3g)***

Yield 83%; m.p. 156-157°C; IR(KBr) cm^{-1}: 3521 (Ar-OH), 2938 (C-H Str.), 3023 (Ar C-H Str.), 1594 (C=N), 1263 (Ar-O-C Str.), 3439 (N-H, str. of cyclic amide), 1790 (C=O, str. of ring), 682 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.08 (1H, dd, -CH_d-), 3.25 (1H, dd, -CH_d-), 3.68 (1H, dd, -CH_e-), 3.51 (1H, s, -CH_c-), 3.70 (s, 3H, -OCH_3), 5.11 (s, 2H, -O-CH_2-), 5.17 (1H, d, -CH_f-), 5.22 (1H, s, Ar-OH), 6.63-7.83 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.32 (C=O), 158.34, 155.58, 149.44, 148.03, 147.01, 141.58, 134.57, 132.68, 130.48, 129.97, 129.21, 127.08, 121.32, 119.47, 117.37, 115.35, 112.14, 111.17, 109.91, 67.12 (-O-CH_2-), 56.10 (-OCH_3), 52.13, 34.77 (-CH_2-) and 29.89 δ; Mass (m/z): 508(M+), 510(M+2); Elemental Analysis: $C_{27}H_{22}Cl_2N_2O_4$; C, 63.62; H, 4.39; N, 5.52%.

3.4.8 6-(4-methoxyphenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones ***(3h)***

Yield 76%; m.p. 139-141°C; IR(KBr) cm^{-1}: 2917 (C-H Str.), 3028 (Ar C-H Str.), 1597 (C=N), 1271 (Ar-O-C Str.), 3443 (N-H, str. of cyclic amide), 1757 (C=O, str. of ring), 680 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.10 (1H, dd, -CH_d-), 3.18 (1H, dd, -CH_d-), 3.54 (1H, dd, -CH_e-), 3.64 (1H, s, -CH_c-), 3.73 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 5.10 (s, 2H, -O-CH_2-), 5.13 (1H, d, -CH_f-), 6.69-7.89 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.43 (C=O), 159.87, 155.46, 149.94, 148.03, 147.03, 142.02, 134.57, 134.64, 133.87, 132.71, 129.77, 127.08, 119.47, 114.25, 112.07, 111.14, 109.96, 67.15 (-O-CH_2-), 56.17 (-OCH_3), 55.62 (-OCH_3), 52.09, 34.49 (-CH_2-) and 29.94 δ; Mass (m/z): 524(M+2); Elemental Analysis: $C_{28}H_{24}Cl_2N_2O_4$; C, 64.31; H, 4.59; N, 5.41%.

*3.4.9 6-(2-nitrophenyl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-ones **(3i)***

Yield 67%; m.p. 178-180°C; IR(KBr) cm^{-1}: 2948 (C-H Str.), 3067 (Ar C-H Str.), 1566 (C=N), 1269 (Ar-O-C Str.), 3447 (N-H, str. of cyclic amide), 1765 (C=O, str. of ring), 684 (C-Cl Str.); ^{1}H-NMR ($CDCl_3$): 3.09 (1H, dd, -CH_d-), 3.32 (1H, dd, -CH_d-), 3.92 (1H, dd, -CH_e-), 3.68 (1H, s, -CH_c-), 3.59 (s, 3H, -OCH_3), 5.04 (s, 2H, -O-CH_2-), 5.24 (1H, d, -CH_f-), 6.78-7.82 (11H, m, -NH-, Ar-H); ^{13}C NMR (400 MHz, DMSO): 177.42 (C=O), 155.52, 149.46, 148.01, 147.06, 145.23, 141.63, 134.46, 133.74, 132.68, 130.54, 129.92, 128.83, 127.08, 123.55, 119.47, 112.14, 111.17, 109.91, 67.10 (-O-CH_2-), 56.12 (-OCH_3), 52.11, 34.78 (-CH_2-) and 30.00 δ; Mass (m/z): 537(M+), 540(M+2); Elemental Analysis: $C_{27}H_{21}Cl_2N_3O_5$; C, 60.19; H, 3.96; N, 7.78%.

3. Conclusion

In the present work, a series of 6-(Aryl)-4-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]-2,3,4,5-tetrahydro-indazol-3-one derivatives **(3a-3i)** were synthesized and characterized. The antimicrobial activities of synthesized indazoles **(3a-3i)** compounds show no moderate to good results compared to standard drug data. The green chemistry approach is also applied for synthesis of indazole derivative of vanillin analogue. Based on analytical data and spectral data, the structure and geometry of different types of indazole derivatives were proposed for each.

Further investigation of compound **3b, 3c** with appropriate structural modification of the above compounds may result in therapeutically useful products. It will be the topic of new research to substitute it with greener reagents, catalyst and solvents, finding more effective anti-fungal and anti-bacterial agents. This work confirms the high importance of heterocyclic compounds in applied fields as reported in many review and research articles.

Acknowledgements

Authors are thankful to the Department of Chemistry of D. K. V. Science college, Jamnagar for providing laboratory facilities. Authors are also thankful to NFDD, Saurashtra University-Rajkot and RSIC Chandigarh for providing ^{1}H NMR and ^{13}C NMR spectral analysis of the compounds and Department of Bio-chemistry, Dr. Subhas University Junagadh for antimicrobial activity of newly synthesized compounds.

References

1. Prakash C. and Singh R., **(2024)** Synthesis of fluorinated six-membered nitrogen heterocycles using microwave irradiation. *Chem. Heterocycl. Comp.*, 60, 216-229. (https://doi.org/10.1007/s10593-024-03323-1).
2. Bastrakov M. A. and Ivanova V. V., **(2024)** Synthesis and reactivity of [1,2,5] thiadiazolo[3,4-*b*]pyridines and [1,2,5]selenadiazolo[3,4-*b*]pyridines. *Chem. Heterocycl. Comp.,* 60, 38–40. (https://doi.org/10.1007/s10593-024-03290-7).
3. Arutiunov, N. A., Zatsepilina, A. M. and Aksenova, A. A., **(2024)** A novel method for the synthesis of 2-arylquinolin-4(1*H*)-ones. *Chem. Heterocycl. Comp.,* 60 275–279. (https://doi.org/10.1007/s10593-024-03333-z).
4. Ren D., Kuang G., & Li X. **(2018)** 1,3-Dipolar cycloaddition of diphenylnitrilimine and 5-arylmethylidene-1-phenyl-1,5,6,7-tetrahydro-4*H*-indazol-4-ones to afford novel spiro[indazole-5,3′-pyrazole] derivatives. *Chem. Heterocycl. Comp.,* 54, 1117–1120. (https://doi.org/10.1007/s10593-019-02401-z).
5. Ladani M. J., Tala S. D., Akbari J. D., Dhaduk M. F., & Joshi H. S., **(2009)** Synthesis and biological study of oxopyrimidines and thiopyrimidines of 2-(2,4-dichlorophenyl) imidazo [1,2-*a*] pyridine 3- carbaldehyde. *Jour. Of Indian Chemical Soc.*, *86*, 104-108.
6. Rokad S. V., Tala S. D., Akabari J. D., Dhaduk M. F., & Joshi H. S., **(2009)** Synthesis, antitubercular and antimicrobial activity of some newN-aryl-1,4-dihydropyridines containing furan nucleas. *Jour. Of Indian Chemical Soc.*, *86*(2), 186-191.
7. Akbari J. D., Tala S. D., Dhaduk M. F., Joshi H. S., Mehta K. B., & Pathak S. J., **(2008)** Synthesis of some new pyrazolo[3,4-*d*] pyrimidines and thiazolo [4,5-*d*] pyrimidines and evaluation of their antimicrobial activities. *Phosphorus, Sulfur, and Silicon,* (183), 1471–1477. (DOI: 10.1080/10426500701681581).
8. Gao M. C., & Xu B. **(2016)** Transition metal-involving synthesis and utilization of N-containing heterocycles: Exploration of nitrogen sources. *Chem. Rec., 16*, 1701–1714.
9. Vidyacharan S., Murugan A., & Sharada D. S. **(2016)** C(sp^2)-H Functionalization of 2*H*-indazoles at C_3-position via palladium(II)-catalyzed isocyanide insertion strategy leading to diverse heterocycles. *J. Org. Chem.,* 81, 2837–2848.
10. Shinde A. H., Vidyacharan S., & Sharada D. S. **(2016)** $BF_3{\cdot}OEt_2$ mediated metal-free one-pot sequential multiple annulation cascade (SMAC) synthesis of complex and diverse tetrahydroisoquinoline fused hybrid molecules. *Org. Biomol. Chem.,* 14, 3207–3211.
11. Behrouz S. **(2017)** Highly efficient one-pot three component synthesis of 2*H*-indazoles by consecutive condensation, C-N and N-N bond formations using Cu/Aminoclay/reduced grapheme oxide nanohybrid. *J. Heterocyclic. Chem., 54*, 1863–1871.

12. Jayanthi M., & Rajakumar P. **(2017)** Synthesis, cell viability, and flow cytometric fluorescence pulse width analysis of dendrimers with indazoles surface unit. *J. Heterocyclic. Chem., 54*, 3042–3050.
13. Lavrard H., & Popowycz F. **(2018)** Regioselective late-stage C-3 functionalization of pyrazolo-[3,4-*b*] pyridines. *Synth.,* 50, 998–1006.
14. Bogonda G., Kim H.Y., & Oh K. **(2018)** Direct acyl radical addition to 2*H*-indazoles using Ag-catalyzed decarboxylative cross-coupling of α-keto acids. *Org. Lett., 20*, 2711–2715.
15. Jones P., Wilcoxen K., Rowley M., & Toniatti C., **(2015)** Niraparib: A poly(ADP-ribose) polymerase (PARP) inhibitor for the treatment of tumors with defective homologous recombination. *J. Med. Chem.,* 58, 3302−3314.
16. Jin C. L., Fang Y. L., Li J. H., Shiow L. P., Jih H. G., & Che M. T. **(2002)** 1-Benzyl – 3 - (5'-hydroxymethyl – 2'-furyl) indazole (YC-1) derivatives as novel inhibitors against sodium nitroprusside - induced apoptosis. *J. Med. Chem.,* 45(23), 4947–49.
17. Steffan, R. J., Matelan, E., Ashwell, M. A., Moore, W. J., Solvibile, W. R., Trybulski, E., ... & Harnish, D. C. (**2004**). Synthesis and activity of substituted 4-(indazol-3-yl) phenols as pathway-selective estrogen receptor ligands useful in the treatment of rheumatoid arthritis. *J. Med. Chem., 47*(26), 6435–38.
18. Giannouli, V., Kostakis, I. K., Pouli, N., Marakos, P., Kousidou, O. C., Tzanakakis, G. N., & Karamanos, N. K. (**2007**). Design, synthesis, and evaluation of the antiproliferative activity of a series of novel fused xanthenone aminoderivatives in human breast cancer cells. *J. Med. Chem.,* 50(7), 1716–19.
19. Elsayed, N. M., Serya, R. A., Tolba, M. F., Ahmed, M., Barakat, K., Abou El Ella, D. A., & Abouzid, K. A. (**2019**) Design, synthesis, biological evaluation and dynamics simulation of indazole derivatives with antiangiogenic and antiproliferative anticancer activity. *Bioorg. Chem.,* 82, 340–359.
20. Jesse A. M., Anura P. D., Paul W. Z., Marsha A. M., & Najam A. S. **(2006)** Oral cholesteryl ester transfer protein (CETP) inhibitors: a potential new approach for treating coronary artery disease. *J. Med. Chem., 49*(1), 318–28.
21. Vincent L., Lee G. E., Lin J., Herman S. H., & Thomas B. **(2001)** Facile Preparation of 3-(1-Piperazinyl)-1H-indazoles. *Lee Org. Proc. Res. Dev., 5*(2), 179–83.
22. Thomas J. S., Leroy J. H., Charles S. D., & Guy S. L., **(2003)** Synthesis and hypotensive activity of a series of 2-substituted 5,6-dimethoxyindazoles. *J. Pharm. Sci., 67*(7), 1022–24.
23. Kym, P. R., Iyengar, R., Souers, A. J., Lynch, J. K., Judd, A. S., Gao, J., ... & Collins, C. A. (**2005**) Discovery and characterization of aminopiperidinecoumarin melanin concentrating hormone receptor 1 antagonists. *J. Med. Chem., 48*(5), 1318–21.
24. Jian X. D., Xiaohong C., Fanying M., Leslie L., Charles H., & Mark M., **(2007)** Potent antitubulin tumour cell cytotoxins based on 3-aroyl indazoles, *J. Med. Chem., 50*(5), 1001–06.
25. Wyrick S. D., Voorstad P. J., Cocolas G., & Hall I. H. **(1984)** Hypolipidemic activity of phthalimide derivatives. 7. Structure-activity studies of indazolone analogues. *J. Med. Chem., 27*(6), 68–72.
26. Arán, V. J., Ochoa, C., Boiani, L., Buccino, P., Cerecetto, H., Gerpe, A., ... & Castellano, E. E. (**2005**) Synthesis and biological properties of new 5-nitroindazole derivatives. *Bioorg. Med. Chem., 13*(9), 3197–3207.
27. El-Hawash, S. A., Badawey, E. S. A., & El-Ashmawey, I. M. (**2006**) Nonsteroidal antiinflammatory agents—part 2 antiinflammatory, analgesic and antipyretic activity of some substituted 3-pyrazolin-5-ones and 1, 2, 4, 5, 6, 7-3H-hexahydroindazol-3-ones. *Eur. J. Med. Chem., 33*(5), 349–61.
28. Soad A. M., Hawash E. L., Sayed E. L., Badawey A. M., & Ibrahim M. **(2006)** El–Ashmawey Nonsteroidal anti-inflammatory agents - part 2 anti-inflammatory, analgesic and antipyretic activity of some substituted 3-pyrazolin-5-ones and 1, 2, 4, 5, 6, 7- 3H - hexahydroindazol-3-ones., *Eur. J. Med. Chem*., 41(2), 155–65.
29. Vyas D. H., Tala S. D., Akbari J. D., Dhaduk M. F., & Joshi H. S. **(2009)** Synthesis, antimicrobial and antitubercular activity of some cyclohexenone and indazole derivatives. *Indian Journal of Chemistry,* 48B, 1405-1410.
30. Wei, W., Liu, Z., Wu, X., Gan, C., Su, X., Liu, H., ... & Ye, T. (**2021**) Synthesis and biological evaluation of indazole derivatives as anti-cancer agents. *RSC Adv.,* 11, 5675-15687.
31. Angelova, V. T., Pencheva, T., Vassilev, N., Simeonova, R., Momekov, G., & Valcheva, V. (**2019**) New indole and indazole derivatives as potential antimycobacterial agents. *Med. Chem. Res., 28*(4), 485–497.