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Synthesis, Antimicrobial Screening and ADME Investigations of Novel Bi-Heterocycles containing Benzopyrones with Pyrazolone

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Few 3-methyl-1-2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetyl-4,5-dihydro-1*H*-pyrazol-5-one derivatives were synthesized and their structures were characterized by FTIR, ^{1}H NMR and mass spectrometry. To assess the potential antibacterial action of a conventional medicine, a biological screening was done on *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*. Furthermore, these medicines underwent *in silico* ADME evaluation. Although all compounds successfully underwent the ADME evaluation, only a limited number of compounds passed the projected toxicity test.

Keywords: 7-Hydroxy-4-methyl-benzopyrone, Cyclization, Pyrazolone, Antibacterial activity, ADME studies.

INTRODUCTION

The varied pharmacological effects of coumarins, particularly their ability to diminish tissue edema and inflammation by lowering the generation and scavenging of ROS implicated in free radical-mediated damage, have gained a great deal of attention in recent years. The antioxidant effects of coumarins have been studied extensively [1], among other things. The fact that coumarins are potent, non-toxic, natural antioxidants capable of scavenging active free radicals like O_2, OH or lipid peroxyl radicals LOO is well established. The core pyrazolone structure, on the other hand, has generally drawn a lot of interest due to its diversity of biological activity, including its antitumor [2], analgesic [3], anti-inflammatory [4], antipyretic [5], antioxidant [6], antiviral [7], antitubercular [8] and antibacterial [9] capabilities. Additionally, the first pyrazolone derivative employed in the treatment of pain and inflammation was antipyrine [10]. Furthermore, pyrazole derivatives like celecoxib and deracoxib are effective analgesics and anti-inflammatory drugs. These include dipyrone, aminopyrine, isopropyl antipyrine, phenyl butazone and oxyphenbutazone. However, because of severe gastrointestinal (GI) side effects, their use has been limited.

In light of these findings, we are carrying on with our research program that focuses on the synthesis of pyrazolone rings that contain heterocyclic moiety [11,12]. Significant progress has been achieved and is continuously being made in the development of innovative anti-inflammatory medications during the past 10 years as a result of several advancements in our understanding of pathogenesis [13]. The antipyrine has shown promise in the treatment of brain ischemia [14], myocardial ischemia [15], fatal neurodegenerative diseases [16], cardiovascular diseases [17]. Similar to coumarin derivatives, synthetic and natural organic chemistry have both been quite interested in them. The biological activity of several products that contain coumarin subunits includes molluscicides [18], anthelmintic, hypnotic, insecticidal [19] action and others are used as anticoagulant agents [20] and fluorescent brighteners. The goal of the current effort is to create and synthesise novel heterocyclic compounds with coumarin moiety because of the significance of the coumarins and pyrazolones stated above. The study also examines the antibacterial activity of the target chemicals.

EXPERIMENTAL

All the chemicals and solvents were procured from Sigma Aldrich, USA. The melting points of the synthesized compounds were measured in the open glass capillary method and are uncorrected. The IR spectra were captured on the Bruker IR spectrometer. Using deuterated dimethyl sulfoxide (DMSO-d_6) and

deuterated chloroform ($CDCl_3$) as solvents and tetramethyl silane as an internal standard, ^{1}H NMR was obtained using a Bruker TD-65536 NMR (400 MHz).

Synthesis of 7-hydroxy-4-methyl-2*H*-chromene-2-one (1): Resorcinol and ethyl acetoacetate undergo Pechmann condensation, yielding 7-hydroxy-4-methyl-chromen-2-one [21].

Synthesis of ethyl 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetate (2): Anhydrous K_2CO_3 (1 g, 5 mmol) and ethyl chloroacetate (1.22 g, 10 mmol) were added to a solution of 7-hydroxy-4-methyl-2*H*-chromen-2-one (1 g, 5 mmol) (**1**) in dry acetone and refluxed for 6 h over a water bath. The reaction mixture was filtered and retained the filtrate, after sometimes crystals will start forming then dry it [22]. Yield: 81-82%; m.p.: 95 ºC; IR (ν_{max}, cm^{-1}): 3319.39 (O-H *str.*), 2922.00 (alkane), 1701.14 (unsaturated ester), 1595.17 (alkene), 1381.11 (C-H *str.*), 1192.55 (C-O *str.*) 1081.47 (C-O *str.*); ^{1}H NMR (DMSO-d_6, 400 MHz): 7.70 (CH-d, 1H) 7.00 (CH-d, C_6-1H, C_8-1H, 2H), 6.23 (CH-s, 1H), 4.93 (CH_2-s, 2H), 4.19 (CH_2, m, 2H), 2.40 (CH_3, s, 3H), 1.24 (CH_3-t, 3H); MS (*m/z*): 262.07; $C_{14}H_{14}O_5$ requires 262.08.

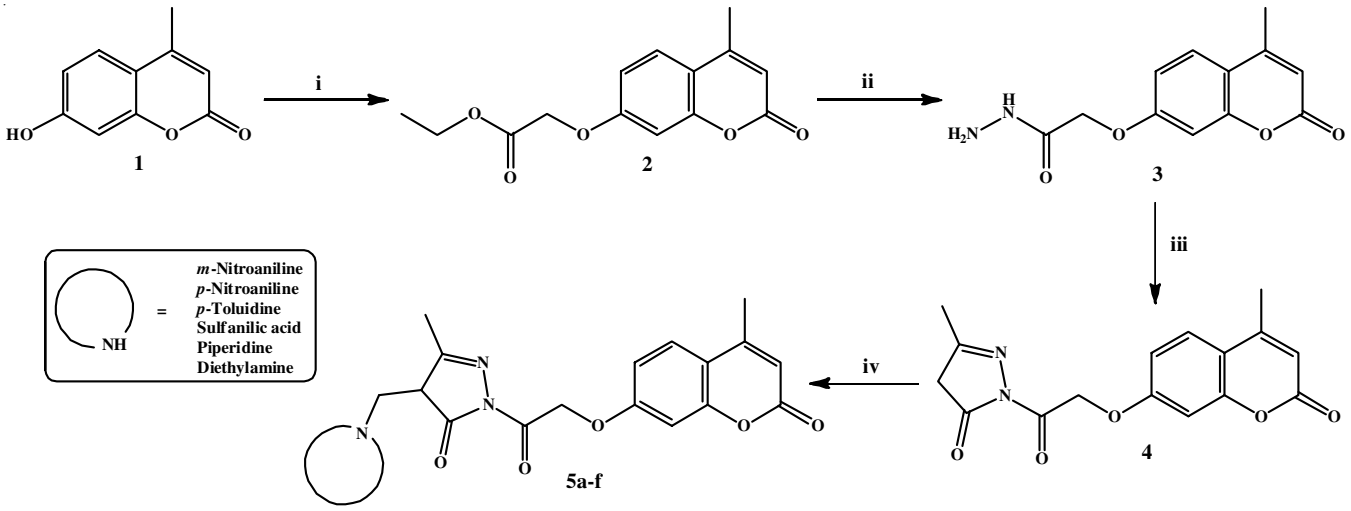
Synthesis of 2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)-acetohydrazide (3): After dissolving in ethanol and refluxing, the crystallized product of compound ethyl[(2-oxo-2*H*-chromen-4-yl)oxy]acetate (1 g, 3 mmol) (**2**) was obtained. Hydrazine hydrate (0.2 g, 5.3 mmol) was added to this solution and the reaction mixture was refluxed for 1 h. After concentrating the reaction mixture, a solid mass separated out and recrystallized using ethanol [22]. Yield 88-90%; colourless solid; m.p.: 202-204 ºC; IR (ν_{max}, cm^{-1}): 3265.80 (N-H *str.*), 1713.22 (C=O *str.*), 1678.14 (C=O *str.*), 1609.04 (C=O *str.*), 1529.53 (N-O *str.*), 1277.13 (C-O *str.*), 1141.83 (C-O *str.*); ^{1}H NMR (DMSO-d_6, 400 MHz): 9.46 (NH-s, 1H), 7.71 (CH-d, 1H), 7.02 (CH-d, 1H), 6.99 (CH-s, 1H), 6.23 (CH-s, 1H), 4.62 (CH_2-s, 2H), 4.37 (NH_2-s, 2H), 2.40 (CH_3-s, 3H); MS (*m/z*): 248.06; $C_{12}H_{12}N_2O_4$ requires 248.08.

Synthesis of 3-methyl-1-{2-[(4-methyl-2-oxo-2*H*-chromen-7-yl) oxy]acetyl}-4,5-dihydro-1*H*-pyrazol-5-one (4): The mixture of 2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetohydrazide (1 g) and ethyl acetoacetate in absolute ethanol was refluxed for 4 h and kept overnight. The resultant solid was filtered and recrystallized from ethanol to give white solid. m.p.: 240-245 ºC; IR (ν_{max}, cm^{-1}): 3147.85 (C-H *str.*), 1715.44 (C=O *str.*), 1609.46 (C=C *str.*), 1489.94 (C=C arom.), 1259.13 (C-O *str.*), 1048.62 (C-O *str.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.59 (CH-d, 1H), 6.98 (CH-m, 1H), 6.81 (CH-s, 1H), 6.20 (CH-s, 1H), 5.09 (CH_2-s, 2H), 3.35 (CH_2-s, 2H), 2.42 (CH_3-s, 3H), 1.94 (CH_3-s, 3H). MS (*m/z*): 314.09; $C_{12}H_{14}N_2O_5$.

Synthesis of pyrazolone derivatives (5a-f): The mixture of 3-methyl-1-{2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetyl}-4,5-dihydro-1*H*-pyrazol-5-one (1 mol. equiv.) was taken with different amines (1 mol. equiv.) with formaldehyde (2 mol. equiv.) and methanol (10-15 mL) was refluxed for 4 to 6 h (**Scheme-I**).

3-Methyl-1-{2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetyl}-4-{[(3-nitro-phenyl)amino]methyl}-4,5-dihydro-1*H*-pyrazol-5-one (5a): Yield: 75%; IR (ν_{max}, cm^{-1}): 3092.53 (N-H *str.*), 2928.16 (C-H *str.*), 2122.98 (C=C *str.*), 1762.08 (C=O *str.*), 1613.31 (C=C *str.*), 1525.84 (N-O *str.*), 1387.26 (CH_3 *bend.*), 1346.82 (NO_2 *str.*), 1268.71 (C-O-C *str.*), 1149.43 (C-OH *str.*), 1015.68 (C-O *str.*), 965.55 (C=C *str.*), 836.82 (C=C *str.*), 738.7 (C-C *str.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.55 CH-d, C_5-1H, (C_2-1H), (C_6-1H) 3H, 7.28 (NH, s (broad), 1H), 6.93 (CH-d, C_6-1H, (C_4-1H), 2H), 6.79 (CH-t, (C_5-1H), 1H), 6.17 (CH-s, C_3-1H, C_8-1H, 2H), 4.72 (CH_2-s, 2H), 3.84 (CH-s, 2H), 3.44 (CH-s, 3H), 2.41 (CH_3-s, CH-s, 4H); *m/z*: 464.13 (100.0%), Elemental analysis of $C_{23}H_{20}N_4O_7$: C, 59.48; H, 4.34; N, 12.06; O, 24.12.

5-Methyl-2-(2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)-acetyl)-4-(((4-nitrophenyl)amino)methyl)-2,4-dihydro-3*H*-pyrazol-3-one (5b): Yield: 75%; IR (ν_{max}, cm^{-1}): 3092.53 (N-H *str.*), 2928.14 (C-H *str.*), 2122.97 (C=C *str.*), 1762.08 (C=O *str.*), 1613.31 (C=C *str.*), 1525.84 (N-O *str.*), 1387.26 (CH_3 *bend.*), 1346.82 (NO_2 *str.*), 1268.71 (C-O-C *str.*), 1149.43 (C-OH *str.*), 1015.68 (C-O *str.*), 965.55 (C=C *str.*), 836.82 (C=C *str.*), 738.7 (C-C *str.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57 CH-d, C_5-1H, (C_2-1H), (C_6-1H) 3H, 7.28 (NH, s (broad), 1H), 6.95 (CH-t,



Scheme-I: (i) Ethyl chloro acetate, K_2CO_3, reflux at 60 °C, 6 h, acetone; (ii) Hydrazine hydrate, ethanol, reflux with stirring, 1 h; (iii) Ethyl acetoacetate, reflux for 4 h, ethanol; (iv) Different amines, formaldehyde, reflux for 6 h, methanol

C_6-1H, C_8-1H, 2H), 6.80 (CH-d, (C_3-1H), (C_8-1H), 2H), 6.17 (CH-s, C_3-1H), 4.73 (CH_2-s, 2H), 3.82 (CH-s, 2H), 3.44 (CH-s, 3H), 2.42 (CH_3-s, CH-s, 4H); *m/z*: 464.13 (100.0%); Elemental analysis of $C_{23}H_{20}N_4O_7$: C, 59.48; H, 4.34; N, 12.06; O, 24.12.

5-Methyl-2-(2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)-acetyl)-4-((*p*-tolyl-amino)methyl)-2,4-dihydro-3*H*-pyrazol-3-one (5c): Yield: 77%; IR (ν_{max}, cm^{-1}): 3095.53 (N-H *str.*), 1699.79 (C=O *str.*), 1610.40 (C=C *str.*), 1559.24 (N-H *bend.*), 1512.77 (N-O *str.*), 1424.51 (N-O bend.), 1387.78, 1369.67 (C-H *bend.*), 1260.44, 1149.55, 1076.20 (C-O *str.*), 1015.42 (C=O *str.*), 847.45 (C-C *str.*), 810.37 (C=C *bend.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57 CH-d, C_5-1H, (C_2-1H), (C_6-1H) 3H, 7.28 (NH, s (broad), 1H), 6.95 (CH-t, C_6-1H, C_8-1H, 2H), 6.80 (CH-d, (C_3-1H), (C_8-1H), 2H), 6.17 (CH-s, C_3-1H), 4.73 (CH_2-s, 2H), 3.82 (CH-s, 2H), 3.44 (CH-s, 3H), 2.42 (CH_3-s, CH-s, 4H), 2.34 (CH_3-s, 3H); *m/z*: 433.16 (100.0%); Elemental analysis of $C_{24}H_{23}N_3O_5$: C, 66.51; H, 5.35; N, 9.69; O, 18.45.

4-(((3-Methyl-1-(2-((4-methyl-2-oxo-2*H*-chromen-7-yl)-oxy)acetyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-amino)benzenesulfonic acid (5d): Yield: 78%; IR (ν_{max}, cm^{-1}): 3080.73 (N-H *str.*), 1014.49, 1147.39 (S=O *str.*), 2978.20 (O-H *str.*), 2121.35 (C-N stretch), 2327.65, 1368.64, 1389.41 (C-H *bend.*), 1559.03, 1510.54 (N-H *bend.*), 1424.12 (CH_2 *bend.*), 1263.28 (C-O *str.*), 1699.01 (C=O *str.*), 1670.04 (C=C *str.*), 845.31 (C-C *str.*), 772.59 (C=C *bend.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57 CH-d, C_5-1H, (C_2-1H), (C_6-1H) 3H, 7.28 (NH, s (broad), 1H), 6.95 (CH-t, C_6-1H, C_8-1H, 2H), 6.80 (CH-d, (C_3-1H), (C_8-1H), 2H), 6.17 (CH-s, C_3-1H), 4.73 (CH_2-s, 2H), 3.82 (CH-s, 2H), 3.44 (CH-s, 3H), 2.42 (CH_3-s, CH-s, 4H), 8.56 (SO_3H, s, 1H); *m/z*: 499.10 (100.0%); Elemental analysis of $C_{23}H_{21}N_3O_8S$: C, 55.31; H, 4.24; N, 8.41; O, 25.62; S, 6.42.

5-Methyl-2-(2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)-acetyl)-4-(piperidin-1-ylmethyl)-2,4-dihydro-3*H*-pyrazol-3-one (5e): Yield: 71%; IR (ν_{max}, cm^{-1}): 3092.55 (N-H *str.*), 2926.23 (C-H *str.*), 1323.72 (C-N *str.*), 1705.15, 1768.13 (-CO-N-, C=O *str.*), 1612.86, 1554.99 (C=O *str.*), 1215.33, 1150.56 (C-O *str.*), 1424.48 (CH_2 *bend.*), 1512.64 (C=C *str.*), 841.73 (C-C *str.*), 743.91 (C=C *bend.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.54 (CH-d, C_5-1H), 6.93 (CH-d, C_6-1H), 6.79 (CH-s, C_8-1H), 6.17 (CH-s, C_3-1H), 4.71 (CH_2-s, 2H), 3.83 (CH-s, 3H), 3.52 (CH-m, 2H), 3.07 (CH-t, CH_2-4H, CH-1H, 5H), 2.41 (CH_3-s, 3H), 2.00 (CH_2-m, 4H), 1.81 (CH_2-t, 2H); *m/z*: 411.18 (100.0%), Elemental analysis of $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21; O, 19.44.

4-((Diethyl amino)methyl)-5-methyl-2-(2-((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)acetyl)-2,4-dihydro-3*H*-pyrazol-3-one (5f): Yield: 75%; IR (ν_{max}, cm^{-1}): 3103.53 (N-H *str.*), 2927.05 (C-H *str.*), 1300.50 (C-N *str.*), 1706.15, 1763.15 (-CO-N-, C=O *str.*), 1612.07, 1556.35 (C=O *str.*), 1200.01, 1149.17 (C-O *str.*), 1424.82 (CH_2 *bend.*), 1512.55 (C=C *str.*), 857.06 (C-C *str.*), 742.07 (C=C *bend.*); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.53 (CH-d, C_5-1H), 6.92 (CH-d, C_6-1H), 6.77 (CH-s, (C_8-1H), 6.14 (CH-s, C_3-1H), 4.70 (CH_2-s, 2H), 3.82 (CH-s, 3H), 3.55 (CH-m, 2H), 3.00 (CH-t, CH_2-4H, CH-1H, 5H), 2.39 (CH_3-s, 3H), 1.88 (CH_3-t, 6H); *m/z*: 399.18 (100.0%); Elemental analysis of $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52; O, 20.03.

Antibacterial activity: By using a disc diffusion technique as described by the Kirby-Bauer method [23], the antibacterial activity of all synthesized pyrazolone derivatives was evaluated on the bacterial cultures of *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa* using the core borer plate method and 10 mg/mL concentrated in DMSO solvent. The antibiotic ampicillin was used as standard and the nutrient agar was used to cultivate the culture in petri dishes for 24 h. The plates were incubated for 24 h at 37 ºC.

RESULTS AND DISCUSSION

The cyclization reaction of benzopyrone derivatives leads to the discovery of the new pyrazolone derivatives with satisfactory yields and characterized. In brief, ester **2** upon hydrazinolysis to produce intermediate **3**. The equivalent pyrazol-5-one (**4**) was synthesized by reacting acid hydrazide (**3**) with ethyl acetoacetate in the presence of absolute ethanol. For C=O groups, the IR spectra showed bands in 1713.22-1609.04 cm^{-1} region. The NH had a band at 3265.80 cm^{-1} in the IR spectra. The C=O bands at 1730-1680 cm^{-1} in compound **3** and the NH peak dispp-eared in compound **4**. The NH_2 and NH peaks of parent acid hydrazide **3** disappeared from the ^{1}H NMR spectra, while a singlet at 1.94 ppm was attributed to CH_3 at C_3 pyrazolone and a signal at 3.35 ppm for CH_2, indicating that compound **3** had undergone cyclization and forms compound **4**. Subsequently, the IR spectra of compounds from **5a** to **5f** revealed bands at 3158-3069 cm^{-1}, which corresponded to the NH band. The signal at 3.35 ppm of CH_2 disappears from the ^{1}H NMR spectra, leaving only a peak at 2.00-3.07 ppm of CH and a peak of CH_2 at 3.00-3.84 ppm. The presence of an NH peak at 7.28 ppm in the ^{1}H NMR spectra of compounds **5a-d** indicates a reaction with aromatic amines, while the elimination of NH peak in compounds **5e** and **5f** indicate a reaction with secondary aliphatic amines.

Antibacterial activity: The biological evaluations were investigated and the results coupled with activity data demonstrated the good antibacterial activity compared to standard ampicillin as shown in Table-1. It was shown that compound **5e** worked best against *Bacillus subtilis* (Gram-positive). Moreover, *Pseudomonas aeruginosa* (Gram-negative) was sensitive to compounds **5c** and **5d**, while *Escherichia coli* (Gram-negative) was sensitive to compounds **5b** and **5f**. As indicated in Table-1, compounds **5a**, **5c** and **5e** were found to be effective against *Staphylococcus aureus* (Gram-positive). Comparing the title compounds to standard ampicillin, they demonstrated strong the inhibitory effects against tested Gram-positive and Gram-negative microorganisms.

ADME studies: The Swiss ADME [24] web server was utilized to determine the physical properties and ADME parameters (absorption, distribution, metabolism and excretion) of a synthesized compounds **3**, **4** and **5a-f** and the results are listed in Table-2. For each chemical, the following five parameters were determined using Lipinski's rule of five: molecular weight (MW) (150 g mol^{-1} < MW < 500 g mol^{-1}), number of hydrogen bond acceptors (nHBA), donors (nHBD), number of rotatable bonds (nRB) and topological polar surface area (TPSA). Lipophilicity (-0.7 < XLOGP3 < 5.0), polarity (20 $Å^2$ < TPSA

TABLE-1
ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**5a-f**)

Compd.	Zone of inhibition (mm)			
	Gram-positive		Gram-negative	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
5a	13	13	12	12
5b	13	12	14	13
5c	13	13	11	15
5d	13	13	10	14
5e	15	15	12	12
5f	13	12	14	11
Control	10	11	10	11

< 130 Å^2), solubility (0 < log S (ESOL) < 6), saturation (0.25 < Fraction Csp3 < 1) and flexibility (0 < of rotatable bonds < 9). These are the criteria that are taken into account to calculate the score. The synthesized molecule **5a-f** displayed a score of 55%, suggesting good bioavailability, in accordance with the rule of five. A log S scale was developed to measure the qualitative solubility of medications that must have a high-water solubility in order to transport active components. If log S is less than -10, it is considered poorly soluble, less than -6, it is moderately soluble, less than -4, it is extremely soluble, less than -2 and less than 0 is highly soluble.

Using the brain or intestine estimated permeation approach (BOILED-Egg), which is provided as a reliable prediction model [25], one may determine the lipophilicity and polarity of tiny substances. Whereas the yellow area represents passive cerebral permeability, the white area represents passive gastric absorption (Fig. 1). The term "topological polar surface area" or TPSA, refers to a substance's capacity to pass through the intestinal wall and cross the blood-brain barrier. For intestinal absorption, a TPSA value of less than 140 is necessary. Compounds **5a-c** were anticipated to be somewhat soluble and compounds **5d-f** to be water-soluble based on this predictive model as shown in Table-2, none of the compounds exhibit blood-brain barrier (BBB) permeation, but the derivatives (**5c-f**) had high GI absorption.

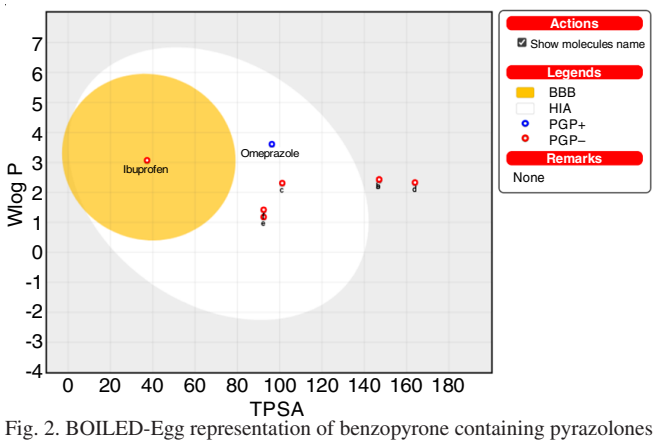


Fig. 2. BOILED-Egg representation of benzopyrone containing pyrazolones with standard ibuprofen and omeprazole

Conclusion

New pyrazolone derivatives (**5c-f**) were synthesized in good yield by condensation of hydrazine and ethyl acetoacetate which further on synthesis with different primary amines and refluxed in methanol. The structure of the synthesized compounds was confirmed by ^{1}H NMR and mass spectrum analysis. When compared to standard ampicillin, the synthesized pyrazolone derivatives demonstrated the potent inhibitory actions against both Gram-positive and Gram-negative bacteria. The ADME (adsorption distribution metabolism excretion) of all the synthesized compounds were predicted by SwissADME. Using the brain or intestinal estimated permeation technique (BOILED-Egg), the GI absorption of the synthesized deriva-

TABLE-2
SWISS ADME RESULTS OF BENZOPYRONE CONTAINING PYRAZOLONES WITH STANDARD IBUPROFEN AND OMEPRAZOLE

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	Ibuprofen	Omeprazole
MW	464.43	464.43	433.36	499.49	411.45	399.45	206.28	345.42
Heavy atoms	34	34	32	35	30	29	15	24
Aromatic heavy atoms	16	16	16	16	10	10	6	15
Fraction Csp3	0.22	0.22	0.25	0.22	0.45	0.43	0.46	0.29
Rotatable bonds	8	8	7	8	6	8	4	5
H-bond acceptors	8	8	6	9	7	7	2	5
H-bond donors	1	1	1	2	0	0	1	1
MR	132.54	132.54	128.68	133.58	123.62	117.02	62.18	93.7
TPSA	147.03	147.03	101.21	163.96	92.42	92.42	37.3	96.31
iLOGP	2.34	2.52	3.13	1.6	3.35	3.14	2.17	2.14
XLOGP3	2.64	2.64	3.17	1.56	2.01	1.9	3.5	2.23
MLOGP	1.02	1.02	2.13	1.36	1.65	1.43	3.13	0.91
Consensus log P	2.08	2.12	3	1.79	2.34	2.26	3	2.41
Consensus log S	-4.2	-4.2	-4.43	-3.73	-3.51	-3.24	-3.36	-3.52
ESOL solubility (mg/mL)	2.91×10^{-2}	2.91×10^{-2}	1.60×10^{-2}	9.30×10^{-2}	1.28×10^{-1}	2.29×10^{-1}	9.09×10^{-2}	1.05×10^{-1}
1GI absorption	Low	Low	High	Low	High	High	High	High
BBB permeant	No	No	No	No	No	No	Yes	No
Pgp substrate	No	No	No	No	No	No	No	Yes
Lipinski violations	1	1	0	1	0	0	0	0
Muegge violations	0	0	0	1	0	0	0	0
PAINS alerts	0	0	0	0	0	0	0	0
Leadlikeness violations	2	2	1	2	1	2	1	0

tives (**5c**, **5e** and **5f**) were found to be high. Because a molecule is blood-brain permeability, there is a possibility that harmful toxicants will enter the circulation and the brain when it is digested. It was anticipated that the other chemicals wouldn't cross the blood-brain barrier.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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