SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME NOVEL 5-(BENZOFURAN-2-YL)-N’-(2-SUBSTITUTED-4-OXOTHIAZOLIDIN-3-YL)-1-PHENYL-1H-PYRAZOLE-3-CARBOXYLAMIDE DERIVATIVES

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ABSTRACT
A series of innovative 5-(benzofuran-2-yl)-N’-(2-substituted-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4a-i) derivatives were synthesized by cyclocondensation reaction of various carbohydrazones (3a-i) with thioglycolic acid in DMF. The intermediate N’-(benzylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazides (3a-i) was obtained by condensation of 5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (1) with various substituted aromatic aldehydes (2a-i) in ethanol. The structures of newly synthesized compounds (4a-i) were corroborated through elemental analysis and spectral studies like IR, ¹H NMR, ¹³C NMR and Mass spectra. The compounds were screened for their in-vitro antibacterial activity against a panel of pathogenic microorganism including gram-negative strains E. coli, P. vulgaris and S. typhi and gram-positive bacterial strain, S. aureus at diverse concentrations and the result of bioassay was compared with Chloramphenicol.

Keywords: Benzylidene, Benzofuran-2-yl, Carbohydrazone, Carbohydrazide, Carboxamide

INTRODUCTION
The availability of an inadequate number of antibiotics for the treatment of infections and incessant development of resistance to the recently used antimicrobial agents has pose a serious challenge as infections caused by micro-organisms are among the foremost causes of death worldwide. As a consequence, the discovery of innovative and potent antimicrobial agents may be the only way to resolve the resistance problem and develop a successful remedy for the dealing of infectious diseases. In search for agents with an improved pharmacokinetic properties, potency or spectrum and lower side effects, heterocyclic derivatives such as thiazolidine-4-ones are found to be one of the important pharmacophores which evoked the sizeable consideration of the chemists in recent few years owing to possess magic moiety because it gives out diverse products possessing potential biological activities and have been identified in the literature as the most promising array of useful pharmacophores in drug design and synthesis.

Thiazolidinones are the derivatives of thiazolidine which belong to one of the most intensively investigated classes of five-member heterocyclic compounds containing sulfur and nitrogen in a five-membered ring. 4-Thiazolidinone ring system is a crucial structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such anti-diabetic,¹ anticancer,²⁻⁵ antiviral,⁶ cytotoxic,⁷⁻⁸ antidepressant, antidiabetic, FSH receptor agonist, antiarrhythmictryanocidal,⁹,¹⁰ anti-HIV agents,¹¹⁻¹³ antimicrobial,¹⁴⁻¹⁶ anticonvulsant,¹⁷⁻¹⁹ antiparkinsonian,²⁰ antimalarial,²¹ anti-inflammatory,²²,²³ pharmacological,²⁴ free radical scavenging,²⁵ CCR4 antagonists,²⁶ antitubercular,²⁷,²⁸

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analgesic, antitumor, antifungal, non-nucleoside inhibitors. The extensive literature survey revealed that incorporation of certain bioactive pharmacophores in the existing drug molecules sometimes exerts a profound influence on the biological profile of that molecule.

In the light of above facts, and to explore this skeleton against several activities and in extension of our efforts in the improvement of novel drugs, the bio potency of these heterocycles impelled us to endure our research to synthesize, 5-(benzofuran-2-yl)-N’-(2-(phenyl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide derivatives utilizing N’-(benzylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide derivatives. Further these synthesized compounds were screened for their in-vitro antimicrobial activity to find compounds having better pharmacological and biological activities.

**EXPERIMENTAL**

**Material and Methods**

All the chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. Melting points were recorded in open capillary tube and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, v max in cm-1). The reactions were monitored by E. Merck TLC aluminum sheet silica gelF254 and visualizing the spot in UV cabinet and iodine chamber. The compounds were analyzed for carbon, hydrogen, nitrogen and sulphur; the results obtained are in good agreement with the expected values obtained by calculation. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet) and m (multiplet). Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micro mass Q-TOF Micro, Mass spectrophotometer. H NMR and C NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d6 as solvent. Elemental analysis (CHN) was done using Thermo Scientific (Flash-2000). All the products obtained were screened for their antimicrobial activities.

**Procedure for the Synthesis of N’-(4-methoxybenzylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (3a-i)**

An equimolar mixture of 5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (10mmol), and substituted benzaldehyde (2a-i) (10mmol) was taken in absolute ethanol (25mL), and then, 2-3 drops of acetic acid was added as a catalyst, the reaction mixture was refluxed for 2h. The resulting mass was allowed to cool, filtered and the product was recrystallized from absolute ethanol to obtained 3a-i (Scheme-1).

**Reaction Scheme : 1**

![Reaction Scheme](image)

*N’-(4-methoxybenzylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazide (3a)*

Pale yellow amorphous solid; mp. 228-230°C; yield, 92%; Rf 0.72; (from absolute ethanol); IR (KBr, v max in cm⁻¹): 3370 (NH str.), 1694(C=O str., amide), 1605(C=N str., azomethine), 1308 (C-N str., amide).
pyrazole), 3143, 3308, 1205, 1256 (C-O-C sym. str.), 1020, 1068 (C-O-C asym. str.), 3068 (CH str., aromatic), 1570, 1508, 1536 (C=C str. aromatic), 1068, 1135 (CH i.p.def., aromatic), 2840 (CH sym. str., aliphatic), 830, 813 (CH o.o.p.def., aromatic), 1458 (CH sym. str., aliphatic), 1458 (CH asym. str. aliphatic).

**1**H NMR δ ppm (DMSO-<sub>d6</sub>): 8.48 (s, 1H, of CH=N), 3.83 (s, 3H, OCH<sub>3</sub> attached to aromatic ring), 7.01-7.67 (m, 15H, aryl and heteroaryl ring), 6.59 (s, 1H, C<sub>4</sub> of pyrazole ring);

**13**C NMR δ ppm (DMSO-<sub>d6</sub>): 146 (s, 1C, CH=N), 144 (s, 1C, C<sub>3</sub> of pyrazole ring), 156.90 (s, 1C, amide CONH), 55.27 (s, 1C, OCH<sub>3</sub>), 160.82 (s, 1C, C of benzene attached to OCH<sub>3</sub>), 153.88 (s, 1C, C<sub>9</sub> of benzofuran ring);

LCMS (m/z), 459[M+Na]<sup>+</sup>, 437[M+1]<sup>+</sup>.

Elemental Anal. Calcd. For C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>; calculated: C, 71.55; H, 4.62; N, 12.84

**Procedure for the Synthesis of 5-(benzofuran-2-yl)-N'-((2-substituted-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4a-i)**

A mixture of carbohydrazone (3a, 0.001M) and thioglycolic acid (0.001M) was taken in a round bottom flask and then to this catalytic amount of fused ZnCl<sub>2</sub> was added. The contents of the flask were refluxed for 8h, cooled, poured on crushed ice, filtered and the product was recrystallized from absolute ethanol to get 4a (Scheme-2). The same procedure was repeated utilizing 3b-i for getting different derivatives from 4b-1.

**Scheme-2**

**Spectral, Elemental and Physical Data of Synthesized Compounds, 4a-i**

5-(benzofuran-2-yl)-N'-((2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4a)

IR (KBr, v<sub>max</sub> in cm<sup>-1</sup>): 3553, 3477, 3391 (NH str., -CONH-), 3068 (C-H str., arom.), 2966 (C-H asym. str., aliphatic), 1505, 1536 (C=C str. arom., 1026, 1070 (C-H i.p.def., arom.), 811, 843 (C-H o.o.p.def., arom.), 1206, 1256 (C-O-C sym. str., ether), 1070, 1026 (C-O-C sym. str., ether), 1693 (CO str., 4-thiazolidinone), 1604 (C=N str.), 700 (C-S-C str.), 1171 (C-N str.), 1693 (CO str. in CONH), 1574 (NH def.).

**1**H NMR δ ppm (DMSO-<sub>d6</sub>): 3.62 (s, 3H, OCH<sub>3</sub> attached to aromatic ring), 3.38 (s, 2H, S-CH<sub>2</sub>-CO, thiazolidinone ring), 6.38 (s, 1H, C<sub>2</sub> of thiazolidinone ring), 6.41 (s, 1H, C<sub>4</sub> of pyrazole ring), 6.83-7.48 (m, 14H, Ar-H + Heteroaryl), 11.60 (s, 1H, of CONH group).

**13**C NMR, δ ppm (DMSO-<sub>d6</sub>): 30 (C<sub>5</sub> of thiazolidinone), 55 (s, 1C of -OCH<sub>3</sub> at C4 of aryl ring), 66 (s, 1C at C<sub>2</sub> of thiazolidinone ring), 105, 107, 111, 114, 121, 123, 124, 125, 126, 127, 128, 129, 135, 139, 144 (s, 1C, C<sub>3</sub> of pyrazole ring), 146, 148, 153 (s, 1C, C<sub>6</sub> of Benzofuran
ring), 156(s, 1C, aromatic carbon atom to which methoxy group attached), 160(s, 1C, amide linkage), 169(s, 1C, C$_4$ of thiazolidinone ring). LCMS (m/z) $510^{[M]}$, $511^{[M+H]}$, $533^{[M+Na]}$; Elemental Anal. Calcd. for C$_{28}$H$_{22}$N$_4$O$_4$S Calculated: C, 65.87; H, 4.34; N, 10.97; S, 6.28 Found: C, 65.80; H, 4.20; N, 10.02; S, 6.46.

5-(benzofuran-2-yl)-N'-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4b)
IR (KBr, $v_{\text{max}}$ in cm$^{-1}$): 3555, 3476, 3395 (NH str., -CONH-), 3065(C-H str., arom.), 2963, (C-H asym. str., aliph.), 2845(C-H sym. str., aliph.), 1453(C-H asym.def., aliph.), 1381(C-H sym.def., aliph.), 1501, 1536(C=C str., arom.), 1029, 1076(C-H i.p.def., arom.), 813, 845(C-H o.o.p.def., arom.), 1200, 1258(C-O-C asym. str., ether), 1076, 1029(C-O-C sym. str., ether), 1694(CO str., 4-thiazolidinone), 1605(C=N str.), 704(C-S-C str.), 1174(C-N str.), 1695(CO str. in CONH), 1577(NH def.).

5-(benzofuran-2-yl)-N'-(2-(2-fluorophenyl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4c)
IR(KBr, $v_{\text{max}}$ in cm$^{-1}$): 3556, 3479, 3395(NH str., -CONH-), 3070(C-H str. , arom.), 2964(C-H asym. str., aliph.), 2845(C-H sym. str., aliph.), 1459(C-H asym.def., aliph.), 1384(C-H sym.def., aliph.), 1506, 1539(C=C str., arom.), 1023, 1074(C-H i.p.def., arom.), 814, 845(C-H o.o.p.def., arom.), 1208, 1259(C-O-C asym. str., ether), 1074, 1027(C-O-C sym. str., ether), 1697(CO str., 4-thiazolidinone), 1607(C=N str.), 700(C-S-C str.), 1175(C-N str.), 1693(CO str. in CONH), 1572(NH def.).

5-(benzofuran-2-yl)-N'-(2-(4-(benzyloxy)phenyl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4d)
IR(KBr, $v_{\text{max}}$ in cm$^{-1}$): 3556, 3479, 3397(NH str., -CONH-), 3062(C-H str., arom.), 2963 (C-H asym. str., aliph.), 2844(C-H sym. str., aliph.), 1455(C-H asym.def., aliph.), 1383(C-H sym.def., aliph.), 1502, 1538(C=C str., arom.), 1023, 1074(C-H i.p.def., arom.), 814, 847(C-H o.o.p.def., arom.), 1204, 1253(C-O-C asym. str., ether), 1074, 1023(C-O-C sym. str., ether), 1695(CO str., 4-thiazolidinone), 1607(C=N str.), 701(C-S-C str.), 1175(C-N str.), 1698(CO str. in CONH), 1577(NH def.).

5-(benzofuran-2-yl)-N'-(4-oxo-2-styrylthiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4e)
IR (KBr, $v_{\text{max}}$ in cm$^{-1}$): 3559, 3473, 3390(NH str., -CONH-), 3062(C-H str., arom.), 2963 (C-H asym. str., aliph.), 2844(C-H sym. str., aliph.), 1455(C-H asym.def., aliph.), 1383(C-H sym.def., aliph.), 1502, 1538(C=C str., arom.), 1023, 1074(C-H i.p.def., arom.), 814, 846(C-H o.o.p.def., arom.), 1202, 1252(C-O-C asym. str., ether), 1074, 1027(C-O-C sym. str., ether), 1694(CO str., 4-thiazolidinone), 1607(C=N str.), 705(C-S-C str.), 1174(C-N str.), 1696(CO str. in CONH), 1577(NH def.).

5-(benzofuran-2-yl)-N'-(2-(furan-2-yl)-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4f)
IR (KBr, $v_{\text{max}}$ in cm$^{-1}$): 3557, 3474, 3395(NH str., -CONH-), 3071(C-H str., arom.), 2968(C-H asym. str., aliph.), 2844(C-H sym. str., aliph.), 1459(C-H asym.def., aliph.), 1383(C-H sym.def., aliph.), 1507, 1539(C=C str., arom.), 1029, 1077(C-H i.p.def., arom.), 816, 842(C-H o.o.p.def., arom.), 1203, 1255(C-O-C asym. str., ether), 1077, 1029(C-O-C sym. str., ether), 1697(CO str., 4-thiazolidinone), 1606(C=N str.), 705(C-S-C str.), 1170(C-N str.), 1694(CO str. in CONH), 1577(NH def.).

Antibacterial Activity
The procedure of agar disc-diffusion method: In-vitro antimicrobial screening was carried out by using Mueller Hinton Agar acquired from Himedia Ltd., Mumbai. The test solution was arranged by dissolving known weight of each compound (4a-i) in dimethyl sulphoxide (DMSO) as a solvent and diluted correctly to give the subsequent concentration of 31-1000µg/mL. Microorganism strains were maintained in nutrient agar medium at 37°C. Petri plates were prepared by pouring 10mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The culture was inoculated in fresh 10mL fresh nutrient broth to yield an initial suspension. The bacterial suspension was diluted ten times with
distilled water. 0.1mL of diluted culture was spread over nutrient agar in the plate. Whatmann No.1 sterile paper discs (6mm) were soaked with a solution and allowed to dry at room temperature. The discs were then applied and then plates were incubated at 37°C for 24h (bacteria) and the zone of inhibition was measured in mm in four directions and expressed as mean. The consequences were compared using Chloramphenicol as a standard drug.

Table-1: Analytical and Physical Data of Synthesized Compound (4a-i)

| Entry | -Ar | Physical Data(4a-i) | Elemental Analysis |
|-------|-----|---------------------|--------------------|
|       |     | M.F : C_{28}H_{22}N_{4}O_{4} | % N Found (Calcd.) |
| 4a    | O   | S                   | N, 10.50 (S, 6.10) |
|       |     | Colour : White solid |                    |
|       |     | M.Pt : 275°C         |                    |
|       |     | Yield : 85%          |                    |
|       |     | Rf. : 0.63           |                    |
|       |     | Recys. S : Ethanol   |                    |
| 4b    | Cl  | M.F : C_{27}H_{19}ClN_{4}O_{3}S | % S Found (Calcd.) |
|       |     | Colour : White solid | N, 10.30 (S, 6.15) |
|       |     | M.Pt : 278°C         |                    |
|       |     | Yield : 82%          |                    |
|       |     | Rf. : 0.65           |                    |
|       |     | Recys. S : Ethanol   |                    |
| 4c    | F   | M.F : C_{27}H_{19}FNO_{3}S | % N Found (Calcd.) |
|       |     | Colour : White solid | N, 11.03 (S, 6.34) |
|       |     | M.Pt : 272°C         |                    |
|       |     | Yield : 80%          |                    |
|       |     | Rf. : 0.68           |                    |
|       |     | Recys. S : Ethanol   |                    |
| 4d    | O   | M.F : C_{29}H_{22}N_{4}O_{4} | % S Found (Calcd.) |
|       |     | Colour : White solid | N, 9.40 (S, 5.36)  |
|       |     | M.Pt : 270°C         |                    |
|       |     | Yield : 83%          |                    |
|       |     | Rf. : 0.67           |                    |
|       |     | Recys. S : Ethanol   |                    |
| 4e    | Ph  | M.F : C_{29}H_{22}N_{4}O_{3} | % N Found (Calcd.) |
|       |     | Colour : White solid | N, 10.95 (S, 6.30) |
|       |     | M.Pt : 274°C         |                    |
|       |     | Yield : 81%          |                    |
|       |     | Rf. : 0.72           |                    |
|       |     | Recys. S : Ethanol   |                    |
| 4f    | O   | M.F : C_{28}H_{18}N_{4}O_{4} | % N Found (Calcd.) |
|       |     | Colour : White solid | N, 11.30 (S, 6.57) |
|       |     | M.Pt : 265           |                    |
|       |     | Yield : 86%          |                    |
|       |     | Rf. : 0.70           |                    |
|       |     | Recys. S : Ethanol   |                    |
RESULTS AND DISCUSSION

In the undertaken research all of the new thiazolidinone derivatives 4a-i was synthesized successfully, with the subsequent aim of finding new compounds with promising antibacterial activities. The synthetic protocol has been outlined in reaction schemes 1 and 2. The physical constants like melting point and solubility were determined for all the intermediate and final products. The newly synthesized compound has been characterized on the basis of spectral data such as $^{13}$C NMR, FT-IR, $^1$H NMR and mass spectra and elemental analysis. At every phase the reaction was monitored with TLC.

The synthesis of target 5-(benzofuran-2-yl)-N'-(2-substituted-4-oxothiazolidin-3-yl)-1-phenyl-1$H$-pyrazole-3-carboxamide derivatives (4a-i) was carried out by reacting $N'$-(benzylidene)-5-(benzofuran-2-yl)-1-phenyl-1$H$-pyrazole-3-carboxhydrazides (3a-i) with thioglycolic acid. IR spectrum of 4a reveals absorption band at 1693 cm$^{-1}$ due to CO str. in thiazolidinone, and stretch at 700 cm$^{-1}$ was observed for C-S-C group, which confirms the cyclisation of carbohydrazone to thiazolidinone. The $^1$H NMR spectrum showed a singlet at $\delta$ 11.60 ppm due to one proton of CONH group and another singlet at $\delta$ 3.38 ppm arises due to two protons of CH$_2$ in S-CH$_2$-CO group of thiazolidinone ring. $^{13}$C NMR approves cyclization into target molecule as a singlet is obtained at 30.38 ppm due to carbon of CH$_2$ of thiazolidinone, yet another singlet at 168 ppm confirms the cyclization to form thiazolidinone molecule 4a. The elemental analysis further gives consistent results with molecular formulae. Mass spectra of 4a shows molecular ion peak M$^+$ at 510 confirming its formation. Thus it was observed that the spectral data such as IR, $^1$H NMR, $^{13}$C NMR and elemental analysis of newly synthesized compound in scheme 2 were in accordance with the proposed structural and molecular formula.

Antibacterial Activity

All the fertile synthesized heterocyclic compounds (4a-i) were tested for their in-vitro antimicrobial activity using agar disc-diffusion method; from the results it is clear that the tested compounds exhibited variable toxicity against different bacteria. This variation in toxicity can be attributed to altered structures and functional groups attached to the basic nucleus presented in table no 1. Results of antibacterial screening indicated that 4a, 4b, 4d, 4h showed good activity against S. aureus and P. vulgaris and the compounds 4a, 4c, 4d, 4f exhibited good activity towards all the selected Gram negative bacterial strains E. coli, P. vulgaris, S. typhi, while rest of the derivatives showed moderate to low activity, when
compared with eminent marketable antibiotic Chloramphenicol. The antibacterial screening data of the compound are presented in Table-2 and 3.

| Compd. Code | Gram +ve | S. aureus | D.M.S.O | Std. Drug |
|-------------|---------|-----------|---------|-----------|
| 4a          | 23      | 19        | 14      | 22        |
| 4b          | 24      | 18        | 17      | 20        |
| 4c          | 20      | 17        | 14      | 12        |
| 4d          | 23      | 20        | 19      | 18        |
| 4e          | 19      | 15        | 16      | 12        |
| 4f          | 22      | 20        | 18      | 17        |
| 4g          | 23      | 20        | 18      | 17        |
| 4h          | 25      | 23        | 20      | 19        |
| 4i          | 18      | 17        | 15      | 12        |
| D.M.S.O     | -       | -         | -       | -         |
| Std. Drug   | 24      | 22        | 20      | 19        |

| Compd. Code | Gram -ve | P. vulgaris | D.M.S.O | Std. Drug |
|-------------|----------|-------------|---------|-----------|
| 4a          | 26      | 23         | 22      | 18        |
| 4b          | 28      | 26         | 19      | 18        |
| 4c          | 24      | 21         | 17      | 16        |
| 4d          | 27      | 23         | 21      | 19        |
| 4e          | 22      | 20         | 19      | 17        |
| 4f          | 23      | 21         | 18      | 15        |
| 4g          | 26      | 24         | 21      | 18        |
| 4h          | 25      | 24         | 22      | 18        |
| 4i          | 20      | 17         | 15      | 12        |
| D.M.S.O     | -       | -          | -       | -         |
| Std. Drug   | 24      | 22         | 20      | 17        |

**Table 2: Antibacterial Activity of the Compounds 4a–i**

**Table 3: Antibacterial Activity of the Compounds 4a–i**

In summary, we have reported the innovative methodology for the synthesis of series of novel 5-(benzofuran-2-yl)-N′-(2-subsituted-4-oxothiazolidin-3-yl)-1-phenyl-1H-pyrazole-3-carboxamide (4a–i) from N′-(benzylidene)-5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carboxyhydrizides (3a–i). The presented series of compounds were synthesized with good yields, without the formation of any unwanted side products. The purity and structure of the newly synthesized compound were confirmed by spectroscopic investigation and chemical analysis. Similarly, these novel compounds were found to be good antibacterial agents.

**CONCLUSION**

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