Synthesis, analgesic, anti-inflammatory and ulcerogenic properties of some novel \(N'-((1-(\text{substituted amino})\text{methyl})-2-\text{oxoindolin-3-ylidene})-4-(2-(\text{methyl/phenyl})-4-\text{o xoquinazolin-3(4}H\text{-yl})\text{benzohydra zide derivatives}}

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ABSTRACT: A new series of \(N'-((1-(\text{substituted amino})\text{methyl})-2-\text{oxoindolin-3-ylidene})-4-(2-(\text{methyl/phenyl})-4-\text{o xoquinazolin-3(4}H\text{-yl})\text{benzohydra zide derivatives 4a-4l were designed and synthesized from anthranilic acid. All the synthesized compounds were characterized by spectroscopic means and elemental analyses. The tail-flick technique and the carrageenan-induced foot paw edema test were performed for screening analgesic and anti-inflammatory activity, respectively. All of the compounds were also examined for their ulcerogenicity. Some of the compounds showed significant activity. Among the test compounds, 4b exhibited 53% and 69% analgesic activity at a dose of 10 and 20 mg/kg, respectively. It also displayed 47% (10 mg/kg) and 65% (20 mg/kg) anti-inflammatory activity with one-fourth of ulcer index of the reference drugs diclofenac and aspirin.

Keywords: Quinazolinone, isatin, schiff base, mannich base, analgesic, anti-inflammatory

1. Introduction

Inflammation is a defensive but exaggerated local tissue reaction in response to exogenous or endogenous insult. It is a fundamental physiological process that is not only essential for survival but at the same time is one of the major causes of human morbidity and mortality (1,2). A large number of non-steroidal anti-inflammatory drugs (NSAIDs) are available clinically to treat inflammatory disorders. NSAIDs are one of the most widely used drug categories against inflammation, mild to moderate pain and fever. In the past decade, numerous advances have taken place in the understanding of pathogenesis and as a result, significant progress has been made and is still being explored for the development of novel NSAIDs (3). Prostaglandin synthetase or cyclooxygenase (COX) is an enzyme which catalyzes the rate limiting steps in the biosynthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins (PGs). The most important mechanism of NSAIDs is considered to be primarily by inhibition of PGs synthesis; specifically competitive inhibition of COX (4). Generally, the NSAIDs inhibit both isomorphisms COX-1 and COX-2. Most NSAIDs are mainly COX-1 selective (e.g., indomethacin, aspirin, ketoprofen, piroxicam, and sulindac). The mechanism of action of celecoxib and rofecoxib is primarily selective inhibition of COX-2 (5). Others are considered to have mixed action on COX-1 and -2 (e.g., ibuprofen, naproxen, diclofenac, etodolac, nabumetone, and meloxicam). Other mechanisms that may contribute to NSAID mediated anti-inflammatory activity include the reduction of superoxide radicals, induction of apoptosis, inhibition of adhesion molecule expression, decrease of nitric oxide synthase, decrease of proinflammatory cytokine levels (tumornecrosis factor-a, interleukin-1), modification of lymphocyte activity, and alteration of cellular membrane functions (6). However, long term clinical usages of NSAIDs are associated with significant side effects such as severe gastrointestinal ulceration, bleeding, intolerance and nephrotoxicity (7,8). Therefore, investigation of new NSAIDs is still a major challenge and production of safer and more active NSAIDs and analgesic drugs are needed.

Quinazoline and quinazolinone nuclei have drawn great attention due to their wide range of chemotherapeutic activities (9-15). Additionally, different known anti-inflammatory drugs such as proquazone I, fluoroquazone II, and tryptanthrin III contain the quinazoline nucleus (Figure 1) (16-19). Also, it has been

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reported that the substitution pattern by different aryl or heteroaryl moieties at 2/3 position of the quinazoline nucleus markedly influences analgesic and anti-inflammatory activity (20).

On the other hand, the indole skeleton exists in a variety of natural products and is the precursor for many pharmaceuticals, such as indomethacin IV, etodolac V, and tenidap VI (Figure 1). In recent decades, the literature has been enriched with progressive findings about synthesis and pharmacological activities of isatin (oxidized form of indole) ring, which is a core structure in various synthetic pharmaceuticals displaying a wide variety of biological activities (21–27).

Based on the above observations and in continuation of our anti-inflammatory and analgesic drug research program (28,29), it was of interest to synthesize a novel series of quinazolinone derivatives with structure modifications involving incorporation of isatin moieties at the 3rd position and a methyl/phenyl group at the 2nd position of the quinazolinone ring as a trial to obtain safer and potent anti-inflammatory and analgesic agents. The ulcerogenic activity of the compounds was also determined.

2. Materials and Methods

2.1. Chemistry

The chemicals and reagents used were obtained from various chemical units Merck India Ltd., Qualigens, CDH, and SD Fine Chem. All solvents used were of laboratory research (LR) grade and purified before use.

All reaction steps were monitored until completion using thin layer chromatography (TLC). An iodine chamber and UV lamp were used for visualization of TLC spots. All melting points were performed in open glass capillary tubes and were uncorrected. 1H-NMR spectra were performed on a Bruker ultra shield (300 MHz) NMR spectrometer in CDCl3 using tetramethylsilane [(CH3)4Si] as an internal standard. Chemical shifts (δ) were expressed as parts per million (ppm). The multiplicities of the signals in the 1H-NMR spectra were abbreviated by s (singlet), t (triplet), q (quartet), and m (multiplet). The J constant was given in Hz. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. All IR spectra were recorded in KBr pellets on a Jasco FT-IR 410 spectrometer. Elemental analyses were performed on a PerkinElmer model 240C analyzer and were within ± 0.4% of the theoretical values.

2.1.1. Synthesis of 2-(methyl/phenyl)-4H-benzo[1,3]oxazin-4-one (1a, 1b)

For the synthesis of the 2-methyl derivative: A mixture of anthranilic acid (1.37 g, 0.01 mol) and acetic anhydride (10.2 mL, 0.1 mol) was refluxed on a gentle flame for 1 h. The excess acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether and was kept aside for 1 h. The light brown solid 1a obtained was filtered and dried (28).

For synthesis of the 2-phenyl derivative: To a solution of anthranilic acid 13.7 g (0.1 mol) dissolved in pyridine (60 mL), benzoyl chloride 28 g (0.2 mol) was added and the mixture was stirred for 30 min at room temperature followed by treatment with 5% NaHCO3 (15 mL). The solid thus obtained 1b was recrystallized from ethanol (29).

2.1.2. Synthesis of 4-(2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl)benzohydrazide (2a, 2b)

A mixture of 2-(methyl/phenyl)-4H-benzo[1,3]oxazin-4-one 1a/1b (1.61/2.23 g, 0.01 mol) and p-aminobenzohydrazide (1.51 g, 0.01 mol) was dissolved in anhydrous pyridine (50 mL) and heated on a sand bath for 10 h. The resulting solution was cooled in an ice bath and treated with dilute hydrochloric acid (100 mL). The product separated 2a/2b was filtered, washed with water, and crystallized from ethanol.

2.1.3. Synthesis of 4-(2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl)-N-(2-oxoindolin-3-ylidene)benzohydrazide (3a, 3b)

Equimolar quantities of 4-(2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl)benzohydrazide 2a/2b (2.94/3.56 g, 0.01 mol) and isatin (1.47 g, 0.01 mol) were dissolved in warm ethanol (30 mL) and heated on...
2.2. Animals

The animals used in the present study were Swiss albino mice weighing 20-25 g and Wistar rats weighing 150-200 g were procured from Bapatla College of Pharmacy, Bapatla, India. Animals were maintained in colony cages at 25 ± 2°C, relative humidity of 45-55%, maintained under 12 h light and dark cycle and were fed standard animal feed (ad libitum) by the oral route for analgesic and anti-inflammatory studies and as a suspension of 10% (v/v) Tween-80 suspension intraperitoneally. One group was administered with aspirin intraperitoneally at a dose of 200 mg/kg once daily for three days. Diclofenac was also administered as a standard drug at 20 mg/kg once daily for three days to another group of animals by the same route. The remaining group of animals was given the test compounds intraperitoneally at a dose of 20 mg/kg. On the fourth day, the pylorus was ligated using the method of Shay et al. (35). Animals were fasted for 36 h before the pylorus ligation procedure. The animals were sacrificed four hours post ligation. The stomach was removed and opened along with the greater curvature. Ulcer index was determined by the method of Ganguly and Bhatnagar (36).

3. Results and Discussion

3.1. Chemistry

The synthetic pathway giving access to the titled compounds 4a-4l is represented in Scheme 1. Initially, 2-(methyl/phenyl)-4H-benzo[1,3]oxazin-4-one was synthesized. The synthetic pathway giving access to the titled compounds 4a-4l is represented in Scheme 1. Initially, 2-(methyl/phenyl)-4H-benzo[1,3]oxazin-4-one was synthesized.
4-one 1a/1b were synthesized from anthranilic acid using acetic anhydride/benzoyl chloride by a simple acetylation/benzyolation followed by a ring closure reaction. In the subsequent step, 4-(2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl)benzohydrazide 2a/2b were synthesized by a simple reaction of compounds 1a/1b with p-aminobenzohydrazide with elimination of a water molecule. Before the final step, Schiff bases 3a/3b were synthesized by nucleophilic addition of the amino derivatives 2a/2b with the carbonyl compound isatin in ethanol. This reaction was followed by dehydration to generate compounds 3a/3b by forming a stable imine. In the last step, the title compounds 4a-4l were synthesized through a Mannich reaction by treating compound 3a/3b with formaldehyde and secondary amines like dimethylamine, diethylamine, diphenylamine, piperazine, morpholine, and piperidine. The physicochemical parameters of all the synthesized compounds are summarized in Table 1. The structures of the synthesized compounds were confirmed by spectral (IR, 1H-NMR, and Mass) and elemental analyses data.

3.2. Analgesic activity

Using Wistar albino mice analgesic activity for title compounds 4a-4l was carried out by the tail-flick technique. The results obtained from the above study are summarized in Table 2. The results of analgesic activity indicate that all the test compounds exhibited a graded dose response and not all of them are significant but some of them gave significant activity. Moreover, this study revealed that test compounds showed moderate analgesic activity at 30 min of reaction time; the activity increased at 1 h, further it reached to peak level at 2 h and it decreased again at 3 h. Compound 4a and 4g with dimethyl substitution showed good activity. With the increased lipophilicity (diethyl group), compounds 4b and 4h showed an increase in activity. Substitution with alicyclic amine (piperidine) in 4f and 4l further increases the lipophilicity and retains the activity of diethyl substitution. The presence of an additional hetero atom such as nitrogen and oxygen in the alicyclic amine rings such as: (piperazine and morpholine) had shown better activity than the rest of the compounds 4c-4l. Substitution with alicyclic amine or aromatic substitution in 4e and 4l showed lower activity. The compounds with aliphatic substitution 4a, 4b, 4g, and 4h had shown better activity than the rest of the compounds 4c-4f and 4i-4l with alicyclic amine or aromatic substitution. Compounds 4b, 4f, 4h, and 4l were found to be the most active analgesic agents and they are almost equal or moderately more potent when compared to the reference standard diclofenac sodium.

Anti-inflammatory activity

Anti-inflammatory activity was performed by the carrageenan-induced paw edema test in rats. The anti-inflammatory activity results (Table 3) showed that all test compounds protected rats from carrageenan-induced inflammation reasonably at 30 min of reaction time; the activity increased at 1 h and it reached the maximum level at 2 h. Declining activity was observed at 3 h. The compounds possessing dimethyl amino substituents 4a
Table 1. Synthesized compounds 4a-4l

<table>
<thead>
<tr>
<th>Compound</th>
<th>-R</th>
<th>-N(R1R2)</th>
<th>Mol. formula</th>
<th>% Yield</th>
<th>Mp (°C)</th>
<th>Rf</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-CH3</td>
<td>-N(CH3)2</td>
<td>C27H24N6O3</td>
<td>75</td>
<td>223-225</td>
<td>0.65</td>
</tr>
<tr>
<td>4b</td>
<td>-CH3</td>
<td>-N(CH3)2</td>
<td>C29H28N6O3</td>
<td>72</td>
<td>256-258</td>
<td>0.72</td>
</tr>
<tr>
<td>4c</td>
<td>-CH3</td>
<td>-N(CH3)2</td>
<td>C37H28N6O3</td>
<td>78</td>
<td>280-282</td>
<td>0.49</td>
</tr>
<tr>
<td>4d</td>
<td>-CH3</td>
<td></td>
<td>C29H27N7O3</td>
<td>70</td>
<td>237-239</td>
<td>0.84</td>
</tr>
<tr>
<td>4e</td>
<td>-CH3</td>
<td></td>
<td>C29H26N6O4</td>
<td>74</td>
<td>244-246</td>
<td>0.58</td>
</tr>
<tr>
<td>4f</td>
<td>-CH3</td>
<td></td>
<td>C30H28N6O3</td>
<td>81</td>
<td>219-221</td>
<td>0.78</td>
</tr>
<tr>
<td>4g</td>
<td>-C6H5</td>
<td>-N(CH3)2</td>
<td>C34H29N7O3</td>
<td>72</td>
<td>252-254</td>
<td>0.61</td>
</tr>
<tr>
<td>4h</td>
<td>-C6H5</td>
<td>-N(CH3)2</td>
<td>C34H28N6O4</td>
<td>71</td>
<td>229-231</td>
<td>0.70</td>
</tr>
<tr>
<td>4i</td>
<td>-C6H5</td>
<td></td>
<td>C35H30N6O3</td>
<td>75</td>
<td>286-288</td>
<td>0.45</td>
</tr>
<tr>
<td>4j</td>
<td>-C6H5</td>
<td></td>
<td>C34H28N6O3</td>
<td>77</td>
<td>248-251</td>
<td>0.54</td>
</tr>
<tr>
<td>4l</td>
<td>-C6H5</td>
<td></td>
<td>C32H26N6O3</td>
<td>70</td>
<td>212-214</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Solvent system used was ethylacetate/hexane/formic acid (4:2:4, v/v).

Table 2. Analgesic activity of the synthesized compounds (Tail-flick method)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td>10</td>
<td>35 ± 0.93*</td>
<td>41 ± 1.36*</td>
<td>45 ± 0.90*</td>
<td>33 ± 0.26*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>46 ± 0.51*</td>
<td>54 ± 0.51**</td>
<td>62 ± 0.33**</td>
<td>37 ± 0.14**</td>
</tr>
<tr>
<td>4b</td>
<td>10</td>
<td>40 ± 1.07**</td>
<td>48 ± 1.16**</td>
<td>53 ± 0.71**</td>
<td>37 ± 0.42**</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>53 ± 0.90*</td>
<td>62 ± 0.48***</td>
<td>69 ± 0.70**</td>
<td>46 ± 1.53*</td>
</tr>
<tr>
<td>4c</td>
<td>10</td>
<td>25 ± 1.64*</td>
<td>29 ± 0.26*</td>
<td>34 ± 1.45*</td>
<td>24 ± 1.72*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>32 ± 1.55*</td>
<td>41 ± 1.21*</td>
<td>44 ± 1.86*</td>
<td>25 ± 1.89*</td>
</tr>
<tr>
<td>4d</td>
<td>10</td>
<td>30 ± 0.78*</td>
<td>36 ± 0.79*</td>
<td>41 ± 1.74*</td>
<td>29 ± 1.40*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>41 ± 1.22*</td>
<td>52 ± 1.37*</td>
<td>56 ± 1.42**</td>
<td>33 ± 1.19*</td>
</tr>
<tr>
<td>4e</td>
<td>10</td>
<td>28 ± 1.63*</td>
<td>35 ± 0.56*</td>
<td>39 ± 1.21*</td>
<td>27 ± 1.82*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>38 ± 0.81*</td>
<td>46 ± 1.16*</td>
<td>50 ± 1.64*</td>
<td>28 ± 1.36**</td>
</tr>
<tr>
<td>4f</td>
<td>10</td>
<td>37 ± 0.96***</td>
<td>47 ± 1.52*</td>
<td>49 ± 0.58**</td>
<td>33 ± 1.18*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>50 ± 1.94*</td>
<td>58 ± 2.02*</td>
<td>66 ± 1.22**</td>
<td>44 ± 0.61**</td>
</tr>
<tr>
<td>4g</td>
<td>10</td>
<td>33 ± 1.69**</td>
<td>38 ± 0.56*</td>
<td>44 ± 0.95*</td>
<td>32 ± 1.29*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>45 ± 0.67*</td>
<td>54 ± 1.27**</td>
<td>60 ± 0.74*</td>
<td>36 ± 1.62**</td>
</tr>
<tr>
<td>4h</td>
<td>10</td>
<td>38 ± 1.60*</td>
<td>47 ± 1.52**</td>
<td>50 ± 1.61*</td>
<td>35 ± 1.18*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>51 ± 0.51**</td>
<td>59 ± 1.41**</td>
<td>68 ± 1.73***</td>
<td>44 ± 1.10*</td>
</tr>
<tr>
<td>4i</td>
<td>10</td>
<td>22 ± 2.12*</td>
<td>27 ± 0.68*</td>
<td>30 ± 1.09*</td>
<td>20 ± 1.76*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>30 ± 1.39*</td>
<td>38 ± 1.67*</td>
<td>43 ± 1.28*</td>
<td>23 ± 0.61*</td>
</tr>
<tr>
<td>4j</td>
<td>10</td>
<td>29 ± 0.67*</td>
<td>34 ± 2.43*</td>
<td>38 ± 1.46*</td>
<td>27 ± 1.39*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>40 ± 0.52*</td>
<td>49 ± 1.16**</td>
<td>53 ± 0.87**</td>
<td>29 ± 1.67*</td>
</tr>
<tr>
<td>4k</td>
<td>10</td>
<td>27 ± 1.38*</td>
<td>33 ± 1.38*</td>
<td>36 ± 0.56**</td>
<td>26 ± 1.57*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>37 ± 1.09*</td>
<td>48 ± 0.69*</td>
<td>51 ± 2.10*</td>
<td>28 ± 0.75*</td>
</tr>
<tr>
<td>4l</td>
<td>10</td>
<td>34 ± 0.81**</td>
<td>45 ± 1.47*</td>
<td>49 ± 1.35**</td>
<td>31 ± 1.80*</td>
</tr>
<tr>
<td></td>
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<td>48 ± 0.64*</td>
<td>55 ± 1.59**</td>
<td>65 ± 0.57**</td>
<td>40 ± 1.52*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>3 ± 0.39</td>
<td>6 ± 0.52</td>
<td>5 ± 0.63</td>
<td>4 ± 0.43</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>10</td>
<td>36 ± 1.52**</td>
<td>43 ± 1.31*</td>
<td>47 ± 1.87**</td>
<td>34 ± 1.16*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>48 ± 0.68*</td>
<td>57 ± 1.47**</td>
<td>63 ± 0.55*</td>
<td>39 ± 0.74**</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SEM (n = 6). Significance levels * p < 0.5, ** p < 0.01, *** p < 0.001 as compared with the respective control.
and 4g exhibited equipotent anti-inflammatory activity to the reference standard diclofenac sodium. With increased lipophilicity, compounds with diethyl amino substituents 4b and 4h showed moderately more potent activity than that of diclofenac sodium. Unlike analgesic activity, the replacement of these alkyl groups with the alicyclic amine (piperazine and morpholine) in 4f and 4l led to a sharp decrease in activity. Placement of an additional hetero substituent (diphenyl amino group) exhibited the least activity. Moreover among the tested compounds, 2-methyl quinazolinone derivatives showed greater analgesic and anti-inflammatory activity than the corresponding 2-phenyl quinazolinone analogs.

### 3.4. Ulcerogenicity

In addition all test compounds were examined for ulcerogenicity and the results are summarized in Table 3. All test compounds exhibited ulcer indexes less than those obtained with the standard diclofenac and aspirin. Results of the ulcer index revealed that compounds bearing alkyl substituents 4a, 4b, 4g, and 4h showed a negligible ulcer index, whereas the replacement of the methyl group with a phenyl group at the 2nd position of the quinazoline ring led to a slight increase in the ulcer index. The other test compounds, 4d-4f and 4j-4l possessing alicyclic amines exhibited a higher ulcer index. The test compounds exhibited 29-57% and 26-51% of the ulcer index when compared to the reference drug diclofenac (1.61 ± 0.53) and aspirin (1.79 ± 0.65), respectively. Among the tested compounds, N-(1-((diethylamino)methyl)-2-oxoindolin-3-ylidene)-4-(2-methyl-4-oxoquinazolin-3(4H)-yl)benzohydrazide 4b exhibited the least ulcer index (0.46 ± 0.24) which is about one-fourth of the ulcer index of the reference standards. Out all of the tested compounds, N'-(1-((diethylamino)methyl)-2-oxoindolin-3-ylidene)-4-(2-phenylquinazolin-3(4H)-yl)benzohydrazide 4j was found to possess the highest ulcer index (0.92 ± 0.60) which is about 54% of the ulcer index of diclofenac and aspirin.

### 4. Conclusion

In summary, a series of N'-((1-(substituted amino)methyl)-2-oxoindolin-3-ylidene)-4-(2-(methyl phenyl)-4-oxoquinazolin-3(4H)-yl)benzohydrazide derivatives 4a-4l were synthesized and characterized...
by IR, ¹H-NMR, mass spectroscopy and elemental analyses. Some of the test compounds exhibited significant analgesic and anti-inflammatory activity with a mild to moderate ulcer index. In general, it was found that 2-methyl quinazolinone analogs showed more potent activity than corresponding 2-phenyl quinazolinone derivatives. Also, quinazoline derivatives bearing alkyl amino groups exhibited the best activity followed by derivatives bearing alicyclic amines whereas derivatives having aryl amino groups showed the least activity. Among all test compounds, N-(1-((diethylamino)methyl)-2-oxoindolin-3-ylidene)-4-(2-methyl-4-oxoquinazolin-3(4H)-yl)benzohydrazide 4b showed the most potent analgesic and anti-inflammatory activity which is more potent than that of the reference diclofenac. From this study we concluded that incorporation of an isatin moiety at the 3rd position and a methyl group at the 2nd position of the quinazolinone ring resulted in potent analgesic and anti-inflammatory activity with a minimal ulcer index. Hence, this analog could be developed as a new class of analgesic and anti-inflammatory agents. However, further structural modification should be planned to enhance their analgesic and anti-inflammatory activities with the low ulcerogenic index.

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References


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Appendix

Characterization data of the synthesized compounds in the current study

2-Methyl-4H-benzo[1,3]oxazin-4-one (1a). Yield: 71%; mp = 182°C; IR (KBr) v max cm⁻¹: 3,096 (Ar-CH₃), 2,882 (CH₂-CH₃), 1,712 (C=O), 1,636 (C-O-Cstr); 1H-NMR (300 MHz, CDCl₃); δ ppm: 2.38 (s, 3H, CH₃), 6.92-7.40 (m, 4H, Ar-H); MS (EI) m/z: 161 [M⁺]; Anal. Calcd. for C₇H₁₀NO₂: C, 75.42; H, 4.05; N, 6.29. Found: C, 76.16; H, 4.40; N, 6.66.

2-Phenyl-4H-benzo[1,3]oxazin-4-one (1b). Yield: 80%; mp = 120°C; IR (KBr) v max cm⁻¹: 3,077 (Ar-CH₃), 1,751 (C=O), 1,625 (C=N), 1,038 (C-O-Cstr); 1H-NMR (300 MHz, CDCl₃); δ ppm: 6.95-7.78 (m, 9H, Ar-H); MS (EI) m/z: 223 [M⁺]; Anal. Calcd. for C₁₄H₁₂NO₂: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.42; H, 4.40; N, 6.29.

4-(2-Methyl-4-oxoquinazolin-3(4H)-yl)benzohydrazide (2a). Yield: 74%; mp = 174-176°C; IR (KBr) v max cm⁻¹: 3,363 (NH₂), 3,038 (Ar-CH₃), 2,932 (CH₂-CH₃), 1,725 (C=O of quinazoline), 1,650 (C=O of amide); 1H-NMR (300 MHz, CDCl₃); δ ppm: 2.53 (s, 3H, CH₃), 3.86 (s, 2H, NH₂), 6.85-7.92 (m, 8H, Ar-H), 9.82 (s, 1H, CONH); MS (EI) m/z: 294 [M⁺]; Anal. Calcd. for C₁₄H₁₄N₂O: C, 65.53; H, 4.78; N, 19.04. Found: C, 65.54; H, 4.78; N, 18.97.

4-(4-Oxoquinazolin-3(4H)-yl)benzohydrazide (2b). Yield: 77%; mp = 159-161°C; IR (KBr) v max cm⁻¹: 3,384 (NH₂), 3,077 (Ar-CH₃), 1,751 (C=O of quinazoline), 1,669 (C=O of amide); 1H-NMR (300 MHz, CDCl₃); δ ppm: 3.74 (s, 2H, NH₂), 7.13-8.09 (m, 13H, Ar-H), 9.85 (s, 1H, CONH); MS (EI) m/z: 356 [M⁺]; Anal. Calcd. for C₁₄H₁₂N₂O: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.99; H, 4.52; N, 15.67.

4-(4-Oxoquinazolin-3(4H)-yl)-N’-(2-oxoindolin-3-ylidene)benzohydrazide (3a). Yield: 70%; mp = 190-192°C; IR (KBr) v max cm⁻¹: 3,368 (NH₂), 3,045 (Ar-CH₃), 2,940 (CH₂-CH₃), 1,733 (C=O of quinazoline), 1,647 (C=O of amide), 1,592 (C=N), 1H-NMR (300 MHz, CDCl₃); δ ppm: 2.60 (s, 3H, CH₃), 7.06-8.20 (m, 12H, Ar-H), 8.94 (s, 1H, NH of isatin), 9.93 (s, 1H, CONH); MS (EI) m/z: 423 [M⁺]; Anal. Calcd. for C₁₄H₁₂N₂O: C, 68.08; H, 4.05; N, 16.54. Found: C, 67.90; H, 4.06; N, 16.60.

4-(4-Oxoquinazolin-3(4H)-yl)-N’-(2-oxoindolin-3-ylidene)benzohydrazide (3b). Yield: 75%; mp = 203-205°C; IR (KBr) v max cm⁻¹: 3,390 (NH₂), 3,034 (Ar-CH₃), 1,747 (C=O of quinazoline), 1,662 (C=O of amide), 1,605 (C=N), 1H-NMR (300 MHz, CDCl₃); δ ppm: 7.28-8.31 (m, 17H, Ar-H), 9.02 (s, 1H, NH of isatin), 9.77 (s, 1H, CONH); MS (EI) m/z: 485

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4-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-N'-(2-oxo-1-piperazin-1-ylmethyl)indolin-3-ylidene)benzohydrazide

IR (KBr) v\textsuperscript{-1} cm\textsuperscript{-1}: 3,376 (NH\textsubscript{str}), 3,066 (Ar-CH\textsubscript{str}), 1,736 (C=O of quinazoline), 1,676 (C=O of amide); 1\textsuperscript{H}-NMR (300 MHz, CDCl\textsubscript{3}): δ ppm: 1.74 (q, J = 5.8 Hz, 3H, CH\textsubscript{3} of quinazoline), 4.36 (d, J = 5.8 Hz, 2H, NCH\textsubscript{2}N), 5.92 (s, 1H, CONH); MS (EI) m/z: 520 [M]+; Anal. Calcd. for C\textsubscript{25}H\textsubscript{23}N\textsubscript{5}O\textsubscript{3}: C, 69.22; H, 5.42; N, 16.14. Found: C, 69.05; H, 5.44; N, 16.18.

N'-(1-(diethylamino)methyl)-2-oxoindolin-3-ylidene)benzohydrazide

IR (KBr) v\textsuperscript{-1} cm\textsuperscript{-1}: 3,393 (NH\textsubscript{str}), 3,084 (Ar-CH\textsubscript{str}), 1,742 (C=O of quinazoline), 1,676 (C=O of amide); 1\textsuperscript{H}-NMR (300 MHz, CDCl\textsubscript{3}): δ ppm: 1.75 (q, J = 5.8 Hz, 3H, CH\textsubscript{3} of quinazoline), 4.32 (d, J = 5.8 Hz, 2H, NCH\textsubscript{2}N), 4.70 (s, 2H, NCH\textsubscript{2}N), 7.10-8.07 (m, 17H, Ar-H), 9.85 (s, 1H, CONH); MS (EI) m/z: 542 [M]+; Anal. Calcd. for C\textsubscript{30}H\textsubscript{28}N\textsubscript{6}O\textsubscript{3}: C, 70.84; H, 4.83; N, 15.49. Found: C, 70.59; H, 4.84; N, 15.55.

N'-(1-(diethylamino)methyl)-2-oxoindolin-3-ylidene)benzohydrazide

IR (KBr) v\textsuperscript{-1} cm\textsuperscript{-1}: 3,409 (NH\textsubscript{str}), 3,058 (Ar-CH\textsubscript{str}), 1,750 (C=O of quinazoline), 1,665 (C=O of amide); 1\textsuperscript{H}-NMR (300 MHz, CDCl\textsubscript{3}): δ ppm: 1.76 (q, J = 5.8 Hz, 3H, CH\textsubscript{3} of quinazoline), 4.34 (d, J = 5.8 Hz, 2H, NCH\textsubscript{2}N), 5.92 (s, 1H, CONH); MS (EI) m/z: 570 [M]+; Anal. Calcd. for C\textsubscript{34}H\textsubscript{30}N\textsubscript{6}O\textsubscript{3}: C, 71.56; H, 5.30; N, 14.73. Found: C, 71.78; H, 5.28; N, 14.69.

4-(2-Methyl-4-oxoquinazolin-3(4H)-yl)-N-(2-oxo-1-piperazin-1-ylmethyl)indolin-3-ylidene)benzohydrazide

IR (KBr) v\textsuperscript{-1} cm\textsuperscript{-1}: 3,370 (NH\textsubscript{str}), 3,085 (Ar-CH\textsubscript{str}), 1,736 (C=O of quinazoline), 1,643 (C=O of amide); 1\textsuperscript{H}-NMR (300 MHz, CDCl\textsubscript{3}): δ ppm: 2.81-3.36 (m, 17H, Ar-H), 9.97 (s, 1H, CONH); MS (EI) m/z: 583 [M]+; Anal. Calcd. for C\textsubscript{22}H\textsubscript{17}N\textsubscript{5}O\textsubscript{3}: C, 70.22; H, 4.99; N, 16.75.

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N’-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzohydrazide (4k).

IR (KBr) $\nu_{\text{max}}$ cm$^{-1}$: 3,385 (NH$_{\text{str}}$), 3,028 (Ar-CH$_{\text{str}}$), 1,739 (C=O of quinazoline), 1,652 (C=O of amide), 1,053 (C-O-C$_{\text{str}}$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ ppm: 2.56 (t, $J$ = 5.6 Hz, 4H, C$_3$C$_5$-CH$_2$ of morpholine), 3.32 (t, $J$ = 6.0 Hz, 4H, C$_2$C$_6$-CH$_2$ of morpholine), 4.46 (s, 2H, NCH$_2$N), 7.05-8.09 (m, 17H, Ar-H), 9.90 (s, 1H, CONH); MS (EI) m/z: 584 [M$^+$]; Anal. Calcd. for C$_{34}$H$_{28}$N$_6$O$_4$: C, 69.85; H, 4.83; N, 14.38. Found: C, 69.64; H, 4.84; N, 14.43.

N’-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)-4-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzohydrazide (4l).

IR (KBr) $\nu_{\text{max}}$ cm$^{-1}$: 3,367 (NH$_{\text{str}}$), 3,033 (Ar-CH$_{\text{str}}$), 1,724 (C=O of quinazoline), 1,670 (C=O of amide); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ ppm: 1.12-1.67 (m, 6H, C$_3$C$_4$C$_5$-CH$_2$ of piperidine), 2.30 (t, $J$ = 5.2 Hz, 4H, C$_2$C$_6$-CH$_2$ of piperidine), 4.61 (s, 2H, NCH$_2$N), 7.22-8.38 (m, 17H, Ar-H), 9.85 (s, 1H, CONH); MS (EI) m/z: 582 [M$^+$]; Anal. Calcd. for C$_{35}$H$_{30}$N$_6$O$_3$: C, 72.15; H, 5.19; N, 14.42. Found: C, 72.41; H, 5.18; N, 14.38.