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Synthesis, *in silico* Biological Profile and MMP-9 Inhibitory Activity of Some Isonicotinic Acid Hydrazide Incorporated Novel Indazoles

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The present study reports the synthesis of isonicotinic acid hydrazide incorporated 7-(substituted benzylidine)-3-aryl-1-(pyridin-4-yl)-methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazoles from substituted chalcones. The chalcones were synthesized by reacting cyclohexanone with a substituted aromatic aldehydes *via* the Claisen-Schmidt method. The IR, ^{1}H NMR and mass spectral studies were used to characterize the synthesized compounds. *In silico* analysis was used to anticipate the biological activities of the synthesized compounds. PASS computer program predicted all title compounds to be anti-inflammatory in nature. All the synthesized compounds were screened for MMP-9 inhibitory activity by the gelatin zymography method. Among all the synthesized compounds **B$_1$**, **B$_3$**, **B$_4$** and **B$_9$** exhibited significant activity whereas rest of the synthesized compounds **B$_2$**, **B$_5$**, **B$_6$**, **B$_7$** and **B$_8$** exhibited mild to moderate anti-inflammatory activity.

Keywords: Chalcones, Indazoles, Biological activity, MMP-9 inhibitory activity.

INTRODUCTION

When tissues are damaged or infected, the body mounts a defence mechanism known as inflammation. It is widely accepted that chronic inflammation plays a pivotal role in the aetiology of many inflammatory diseases, including cancer. Cancer kills roughly 10 million people in the world by year 2020 [1-3]. Multiple studies [4-6] demonstrated that inflammatory cells matrix metalloproteinase (MMP) secretion promotes tumour initiation and spread. Colorectal tumors, breast cancer, gastric carcinoma, pancreatic carcinoma, oral cancer, melanoma, malignant gliomas, chondrosarcoma and gastrointestinal adenocarcinoma are all examples of invasive and extremely tumorigenic malignancies with elevated expression of MMP-9 and MMP-2.

Literature showed a correlation between elevated MMP-9 and plaque instability, rupture and further progression. All of these factors amplify the inflammatory response, which in turn boosts the development of atherosclerosis and the probability of atherothrombosis and coronary events [7-10]. As a result, MMP-9 is now being studied as a potential medicinal target; blocking MMP-9 activity has been shown to have anti-inflammatory, anticancer, anti-metastatic effects, *etc*.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of therapy for mild pain, as outlined by the World Health Organization's (WHO) analgesic ladder for the management of cancer pain. Although nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed, there is some evidence to suggest that people with acute viral respiratory infections (including COVID-19) are at greater risk for adverse effects when taking these medications [11-15]. Therefore, there is a need to search for new anti-inflammatory agents.

Indazoles (benzpyrazoles) belong to an important group of heterocycles that display interesting biological properties such as anti-inflammatory, analgesic, anticancer, antibacterial, antifungal, antitubercular and antiparasitic activities [16-25]. Hydrazine derivatives (N-N fragment) readily react with α,β-unsaturated carbonyl compounds, β-diketones, β-ketoesters and cyanoacetic esters to give indazoles, usually in good yields [26,27]. Several nitrogen-containing bioactive heterocyclic compounds, such as indazole derivatives have already been reported in the literature [28-32]. In present study, the nitrogen

containing fragment is isonicotinic acid hydrazide (N-N fragment hydrazine) and 2,6-*bis*-substituted benzylidene cyclohexanone (chalcone) serves as an excellent illustrative example in that it readily undergoes the conden-sation reaction with isonicotinic acid hydrazide (INH) to produce the title compounds in good yield.

In view of these observations in this work, 7-(substituted benzylidene)-3-aryl-2,3,4,5,6,7-hexahydroindazol-1-yl(pyridin-4-yl)methanones were synthesized and screened for their anti-inflammatory activity.

EXPERIMENTAL

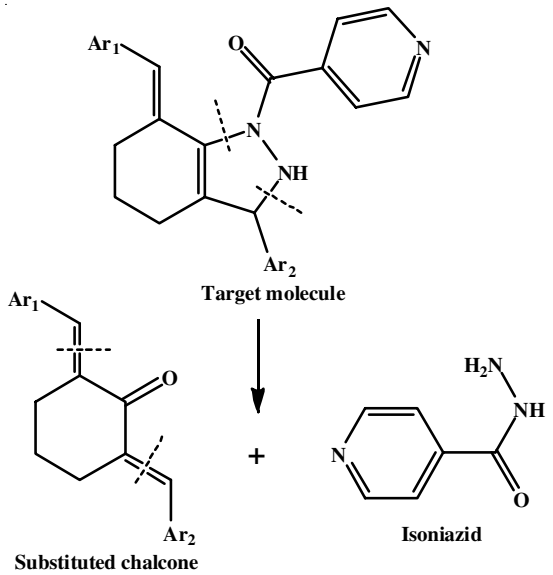
The chemicals used in this work were procured from the commercial sources and used without further purification. The melting points were determined in an open capillary tube using digital melting point apparatus and are uncorrected. Using chloroform:acetone (2:1), TLC was used to determine the homogeneity and purity of the compounds on silica gel GF-254 plates. The infrared spectra were recorded on a Shimadzu FT-IR 6000 using KBr discs. The Perkin-Elmer Series II 2400 CHNS/O Elemental Analyzer was used to conduct the CHNO elemental analysis. Direct insertion probe method was used to obtain mass spectra on the JEOL GC Mate II GC-Mass spectrometer at 70 eV. Using a BRUKER AVIII-500 MHz FT NMR spectrometer, ^{1}H NMR spectra were recorded with DMSO-d_6 as solvent and TMS as internal standard.

Retro-synthetic analysis (RSA): In this method, the synthetic target undergoes a deconstruction or disconnection process, analogous to the reversal of a synthetic reaction, in order to be converted into simpler precursor structures (synthons) with no prior knowledge of the beginning materials. To get to simple or widely available structures, the process is repeated with each new set of precursors generated.

Using RSA, we were able to produce α,β-unsaturated carbonyl compound (2,6-*bis*-substituted benzylidene cyclohexanone-chalcone) and isonicotinic acid hydrazide by breaking apart the two C-N bonds of indazole (INH). Aryl aldehydes and cyclohexanone are the products of α,β-unsaturated carbonyl compound (**Scheme-I**).

Synthesis of 2,6-*bis*(substituted benzylidene)cyclohexanones: Aqueous NaOH solution (70%, 5 mL) was added dropwise while stirring a reaction mixture of cyclohexanone (1 mL, 0.01 mol) and substituted aromatic aldehydes (0.02 mol) in absolute ethanol (50 mL) cooled to 5-10 ºC. Overnight, the reaction mixture was allowed to stand while being stirred for an additional 2 h. After the solution was neutralized with conc. HCl, the precipitate was filtered, rinsed in cold water until the washings were no longer acidic to the litmus test, and then recrystallized in hot water **(Scheme-II)**.

Synthesis of (7-(substituted benzylidene)-3-(substituted phenyl)-2,3,4,5,6,7-hexahydroindazole-1-yl)(pyridin-4-yl)-methanone (B_1-B_9): The reaction mixture consisted of 0.01 mol of 2,6-bis-substituted benzylidene cyclohexanone, 1.37 g of isoniazid (**2**) and 50 mL of ethanol, which was refluxed for 6 h in pyridine medium. The reaction mixture was slowly poured into a container of pulverised ice while being continuously stirred. Absolute ethanol was used to recrystallize the crude material. The TLC with a mobile phase consisting of acetone:chloroform (1:2) solvent system was used to determine the purity of the compound (**Scheme-II**).



Scheme-I: Retrosynthetic analysis of title compounds B_{1-9}

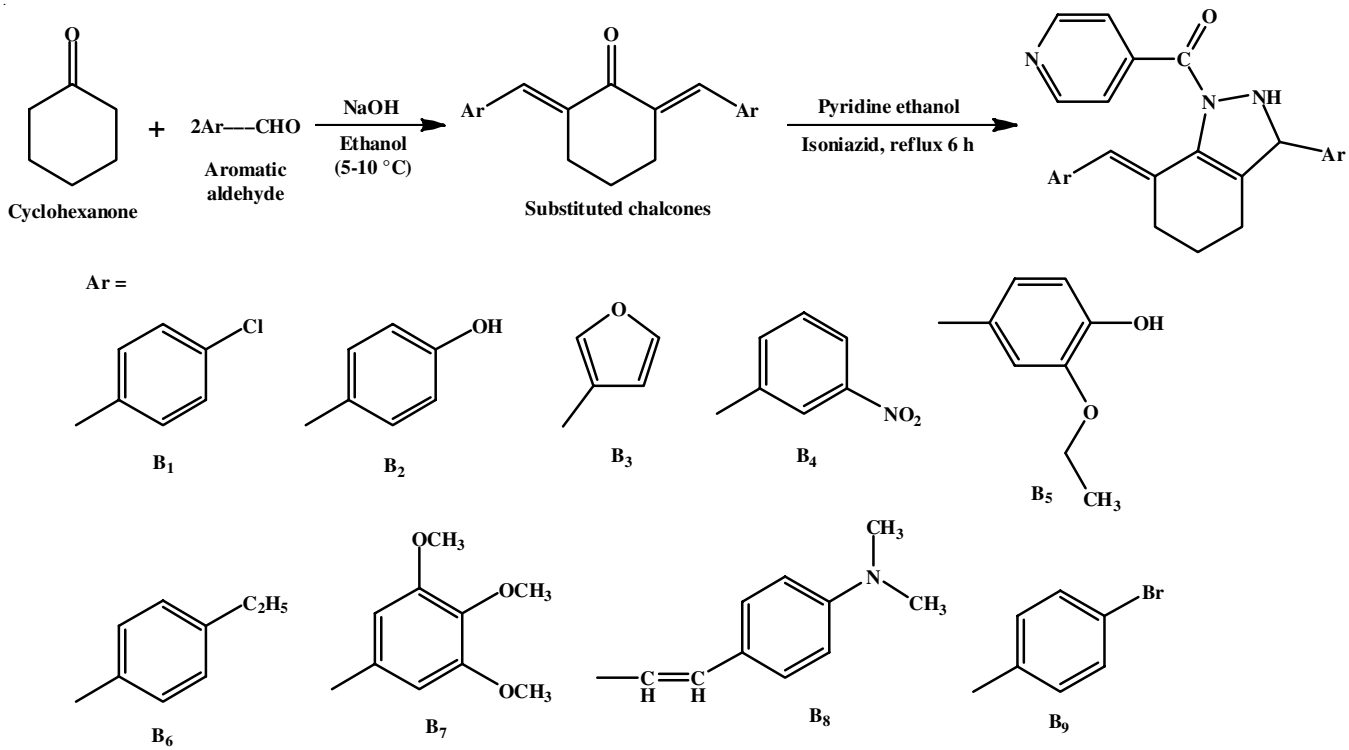
7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-1-(pyridine-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_1): Yield: 95%, m.p.: 125-130 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1668.63 (C=O *str.*), 1672.49 (C=C arom.), 1356.12 (C≡N *str.*), 2966.88 (C-H *str.*), 1608.60 (N-H *str.*), 690.60 (C-Cl *str.*); Mass *m/z* 462.37; ^{1}H NMR (DMSO-d_6, δ ppm): 1.37 (4H, m, $2CH_2$), 2.1 (2H, m, CH_2), 4.59 (1H, d, CH), 2.49 (1H, s, NH), 7.15 (8H, m, aromatic), 9.06 (4H, m, C_5H_5N).

7-(4-Hydroxybenzylidene)-3-(4-hydroxyphenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_2): Yield: 85%, m.p.: 285-289 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1662.47 (C=O *str.*), 1677.35 (C=C arom.), 1336.83 (C≡N *str.*), 2970.74 (C-H *str.*), 1633.91 (N-H *str.*), 3568.74 (OH *str.*); Mass *m/z* 425.47; ^{1}H NMR (DMSO-d_6, δ ppm): 1.96 (4H, m, $2CH_2$), 2.41 (2H, m, CH_2), 4.34 (1H, d, CH), 2.40 (1H, s, NH), 5.0 (2H, m, OH), 7.89 (8H, m, aromatic), 8.96 (4H, m, C_5H_5N).

7-(Furan-3-ylmethylidene)-3-(3-furan-3-yl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_3): Yield: 91%, m.p.: 140-144 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1665.37 (C=O *str.*), 1645.48 (C=C arom.), 1344.55 (C-N *str.*), 2963.03 (C-H *str.*), 1641.62 (N-H *str.*), 1186.37 (C-O*str.*); Mass *m/z* 373.40; ^{1}H NMR (DMSO-d_6, δ ppm): 1.45 (4H, m, $2CH_2$), 2.3 (2H, m, CH_2), 4.59 (1H, d, CH), 2.0 (1H, s, NH), 7.23 (6H, m, Furan), 7.96 (4H, m, C_5H_5N).

7-(3-Nitrobenzylidene)-3-(3-nitrophenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_4): Yield: 83%, m.p.: 290-295 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1668.63 (C=O *str.*), 1653.20 (C=C arom.), 1325.26 (C-N *str.*), 2955.31 (C-H *str.*), 1645.48 (N-H *str.*), 1506.59 (C-NO_2), 1525.88 (N-O *str.*); Mass *m/z* 483.47; ^{1}H NMR (DMSO-d_6, δ ppm): 1.37 (4H, m, $2CH_2$), 2.1 (2H, m, CH_2), 4.59 (1H, d, CH), 2.40 (1H, s, NH), 7.47 (8H, m, arom.), 8.98 (4H, m, C_5H_5N).

7-(3-Ethoxy-4-hydroxy-benzylidene)-3-(3-ethoxy-4-hydroxyphenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-



Scheme-II: Synthetic route of 2,6-*bis*(substituted benzylidene)cyclohexanones and title compounds $\mathbf{B_{1\text{-}9}}$

hexahydro-1*H*-indazole (B_5): Yield: 89%, m.p.: 278-282 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1660.91 (C=O *str.*), 1645.48 (C=C arom.), 1348.41 (C-N *str.*), 2974.60 (C-H *str.*), 1630.05 (N-H *str.*); Mass *m/z* 569.60; ^{1}H NMR (DMSO-d_6, δ ppm): 1.36 (4H, m, 2 × CH_2), 2.1 (2H, m, CH_2), 4.59 (1H, d, CH), 3.733 (6H, s, CH_3), 2.02 (1H, s, NH), 6.28 (2H, m, OH), 6.98 (6H, m, arom.), 7.87 (4H, s, C_5H_5N).

7-(4-Ethylbenzylidene)-3-(4-ethylphenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_6): Yield: 92%, m.p.: 120-124 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1665.43 (C=O *str.*), 1626.19 (C=C arom.), 1329.12 (C-N *str.*), 2966.88 (C-H *str.*), 1622.33 (N-H *str.*), 2970.74 (C-C *str.*); Mass *m/z* 449.58.

7-(3,4,5-Trimethoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_7): Yield: 88%, m.p.: 130-136 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1669.18 (C=O *str.*), 1626.48 (C=C arom.), 1346.21 (C-N *str.*), 2937.67 (C-H *str.*), 1630.05 (N-H *str.*), 2829.92 (C-C *str.*); Mass *m/z* 573.63.

7-[4-(Dimethylamino)phenyl)prop-2-en-1-ylidene]-3-[4-(dimethylamino)phenyl)ethenyl]-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B_8): Yield: 90%, m.p.: 285-288 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1660.91 (C=O *str.*), 1626.48 (C=C arom.), 1359.98 (C-N *str.*), 2955.31 (C-H *str.*), 1641.62 (N-H *str.*), 1292.46 (C-N *str.* Ar-NH_2); Mass *m/z* 531.69.

7-(4-Bromobenzylidene)-3-(4-bromophenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (B9): Yield: 85%, m.p.: 285-288 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1661.94 (C=O *str.*), 1672.49 (C=C arom.), 1356.73 (C-N *str.*), 2966.88 (C-H *str.*), 1608.94 (N-H *str.*), 508.80 (C-Br *str.*); Mass *m/z* 567.31.

***in silico* Biological activity profile:** *in silico* Drug discovery and development now routinely employs the practise of predicting the biological action in connection to the chemical structure of a compound. The biological activity spectrum of a substance can be predicted from its structural formula using the programme Prediction of Activity Spectra for Substances (PASS) [33]. It helps in finding most probable new leads with required activity spectra among the compounds from in-house and commercial data bases. Therefore, all the title compounds ($\mathbf{B_{1\text{-}9}}$) SMILES (Simplified Molecular Input Linear Entry System) notations were entered in PASS, among those possible biological activities the compounds showed more probability to be active for analgesic, anti-inflammatory and Alzheimer's disease treatment.

Anti-inflammatory activity (gelatin zymography method): Gelatin zymography [34] was used as the basis for performing the SDS-PAGE. In order to perform electrophoresis, a zymogram gel was made up of 7.5% polyacrylamide gel copolymerized with gelatin (1 mg/mL). The SDS was removed by washing the gel three times for 1 h each with 50 mL of 2.5% (v/v) Triton X-100 in purified water. The gel was then exposed to a developing solution (consisting of $CaCl_2$ (10 mM), Triton X-100 (1%), and Tris buffer (50 mM, pH 7.4) for 18 h at 32 ºCelsius. Additionally, the rings were visible after the gel was stained for 2 h with Coomassie brilliant blue R250 and then left for another 24 h. The gel rings demonstrate the inhibitory effects of the synthesized compounds on MMP-2 and MMP-9.

RESULTS AND DISCUSSION

Novel 7-(substituted benzylidine)-3-aryl-1-(pyridin-4-yl)-methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazoles compounds

(**B_{1-9}**) were synthesized according to **Scheme-II**. All the synthesized compounds were obtained as crystalline needles with sharp melting points. The yields of the product were found to be satisfactory. All the synthesized compounds show the characteristic peaks in the FT-IR and NMR spectra. Expected molecular ion peak (M+) fragments were observed for the synthesized compounds in mass spectra.

Table-1 displays the PASS-predicted bands of biological activity. Probabilities of revealing and concealing specific kinds of biological activity are computed. Both the Pa and Pi numbers, which ranged from 0 to 1, were arbitrary and unrelated. In case of the biological activities, it is reasonable to assume that the compound will only show those activities where Pa > Pi. The action of the compound is more likely to be revealed in the experiment if Pa > 0.7, but in this case, it is more likely to be an analogue of the known pharmaceutical agent. This action is not likely to be observed in the experiment if Pa < 0.5, but if it is observed, the compound may represent a novel chemical entity. It is noteworthy to observe that despite the fact that all the synthesized compounds had a predicted Pa < 0.5 for anti-inflammatory activity, they all showed significant activity in the experiment.

TABLE-1
PREDICTED BIOLOGICAL ACTIVITY SPECTRUM OF TITLE COMPOUNDS (**B_{1-9}**)

Compd.	Pa	Pi	Activity
B_1	0.490	0.013	Alzhemer's disease treatment
	0.304	0.116	Analgesic
	0.331	0.135	Anti-inflamatory
B_2	0.471	0.016	Analgesic
	0.222	0.188	Alzhemer's disease treatment
	0.158	0.097	Anti-inflamatory
B_3	0.375	0.036	Alzhemer's disease treatment
	0.170	0.076	Anti-inflamatory
	0.141	0.097	Liver fibrosis treatment
B_4	0.642	0.005	Alzhemer's disease treatment
	0.180	0.042	Insulin inhibition
	0.179	0.143	Anti-inflamatory
B_5	0.506	0.078	Antineoplastic
	0.342	0.012	Alzhemer's disease treatment
	0.168	0.128	Antiepileptic
B_6	0.474	0.043	Anti-asthamatic
	0.420	0.046	Anti-inflamatory
	0.196	0.015	Alzhemer's disease treatment
B_7	0.270	0.179	Anti-inflamatory
	0.267	0.087	Alzhemer's disease treatment
	0.182	0.169	Anti-tuberculosic
B_8	0.406	0.098	Antineoplastic
	0.164	0.027	Alzhemer's disease treatment
	0.124	0.087	Antiepileptic
B_9	0.406	0.164	Antiviral
	0.379	0.164	Antineoplastic
	0.250	0.027	Alzhemer's disease treatment

Isolated tonsil tissue was used in a gelatin zymography assay to test each synthetic indazole for its anti-inflammatory action (MMP-2 and MMP-9 inhibitory activity). During chronic inflammation, which includes a series of complex morphological changes in cell barrier, cell-cell interaction and cell matrix interaction, MMPs and MMP-9 in particular, are important regulators of extracellular matrix (ECM) and convert the inflammatory cells. In this research, the synthesized compounds were tested if they could reduce the inflammation by blocking MMP-9. The evidences from the gelatin zymography indicated that the aforementioned substances have an anti-MMP-2 and anti-MMP-9 effect. However, more genetic research is needed to determine how exactly they reduce inflammation.

Among all the synthesized compounds **B_1**, **B_3**, **B_4** and **B_9** exhibited significant MMP-9 activity inhibitory activity whereas remaining compounds **B_2**, **B_5**, **B_6**, **B_7** and **B_8** exhibited mild to moderate anti-inflammatory activity in gelatin zymography method (Table-2). The results of this evaluation have been compared by taking tetracycline as reference standard.

TABLE-2
PERCENTAGE OF MMP-9 INHIBITORY ACTIVITY OF TITLE COMPOUNDS (**B_{1-9}**)

Compd.	Activity (%)	Compd.	Activity (%)	Compd.	Activity (%)
B_1	90	**B_4**	95	**B_7**	72
B_2	80	**B_5**	75	**B_8**	70
B_3	92	**B_6**	85	**B_9**	90

It is clear that compound **B_4** was found to be the most potent. Compounds **B_3**, **B_1** and **B_9** were found to be slightly less potent than **B_4**, followed by compounds **B_6**, **B_2**, **B_5**, **B_7** and **B_8**, respectively. The MMP-9 inhibitory activity of the synthesized compounds in the order of their increasing potency are **B_4 > B_3 > B_1**, **B_9 > B_6 > B_2 > B_5**, **B_7** and **B_8**.

Compound **B_4** bear *para*-nitrophenyl group at 3rd and *para*-nitrobenzylidene group at 7th position of indazole nucleus. Compound **B_3** carry heterocyclic furan ring at 3rd and furanyl-methylidene group at 7th position of indazole moiety. The compounds having electron withdrawing groups in the benzene ring located at 3rd and 7th position of indazole moiety have remarkably more activity than the remaining compounds. From the results, it has been revealed that the compound should have electron withdrawing groups at *para* position of benzene ring or an unsubstituted heterocyclic ring at 3rd and 7th position of indazole for maximal activity. The mono-substitution on benzene ring located at 3rd and 7th position of indazole moiety and electron withdrawing moiety of moderate to bulkier size at *para*-position of benzene seems favourable for the MMP-9 inhibitor activity.

Conclusion

A new series of isonicotinic acid hydrazide (INH) incorporated indazoles (**B_{1-9}**) were synthesized and characterized successfully. Most of the synthesized compounds exhibited a promising MMP-9 inhibitory activity. Among the series, 7-(3-nitrobenzylidene)-3-(3-nitrophenyl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (**B_4**) and 7-(furan-3-yl-methylidene)-3-(3-furan-3-yl)-1-(pyridin-4-yl)methanone)-2,3,4,5,6,7-hexahydro-1*H*-indazole (**B_3**) emerged as the most active as they show percentage of activity 95 and 92, respectively. According to the structural activity relationship studies, by introducing electron pullers on phenyl ring and incorporating INH in indazole nucleus can increase MMP-9 inhibitory activity.

Further research on analogues with a different electron modulators on phenyl or aryl rings could result in far more potent anti-inflammatory agents. However, further studies are required to establish the mechanism of action of title compounds. The contributing physico-chemical properties for MMP-9 inhibitory activity need to be established by detailed quantitative structure activity relationship studies, which may provide insights into the structural requirements of this class of molecules.

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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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