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SYNTHESIS AND 2D-QSAR STUDY OF SOME NOVEL SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS ANTITUBERCULAR AGENTS

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Keywords:

Benzimidazole, Antitubercular activity, MABA, 2D-QSAR, MLR, PLS

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ABSTRACT: In the present work, a series of some novel substituted benzimidazole derivatives were efficiently synthesized, and a thin layer chromatography study confirmed the completion of the reaction on silica gel-G plates. The characterization was done through recording spectra of FTIR using Jasco FTIR-460 plus spectrophotometer, recording spectra of ^{1}HNMR with the help of spectrometer, specifically BRUKER 400MHz. The synthesized substituted novel benzimidazole derivatives were screened for their *in-vitro* antitubercular activity by the Microplate Alamar Blue Assay (MABA) method against *Mycobacterium tuberculosis* (H37Rv strain) with their 2D-QSAR studies. The antitubercular activity results confirmed that compounds DPK3d1, DPK2d1, DPK2d2, DPK2d3, DPK4B1d2, DPK4B2d1, and DPK4B2d2 had shown potent antitubercular activity as compared to standard drugs. These synthesized derivatives were selected 2D-QSAR analysis with their different models such as multiple linear regression (MLR), and partial least squares regression (PLR) analysis were generated to find out the correlation between physicochemical properties parameters and their biological activity. 2D-QSAR models such as MLR and PLS method studies generated an equation showing that descriptors SsOHcount, Ipc Average, Delta AlphaA, Delta AlphaB, and chi6chain are directly proportional to the antitubercular activity. The prediction activity in the test set is rewarding for the development of antitubercular therapy.

INTRODUCTION: Tuberculosis is a deadly disease usually caused by *Mycobacterium tuberculosis*. It has killed an estimated one billion people over the last two spans and is still among the top ten causes of death in the world. According to the 2018 report of WHO, 5, 58,000 people developed rifampicin-resistant (RR TB), multidrug-resistant tuberculosis (MDR-TB), or extensively drug-resistant (XDR TB) in the world. For these necessities, researchers can develop novel chemotherapeutic agents. These different entities have shortened the duration of action and delay the resistance of several infectious diseases [1, 2, 3, 4].

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Benzimidazole is a lead molecule for most of the biological agents used in the pharmaceutical industry. It consists of a fused benzene ring with heterocyclic aromatic imidazole [5, 6, 7, 8]. The existence of imidazole creates it resourceful heterocycles with an extensive range of biological activities such as antiulcer (Gastric H^{+}/K^{+}-ATPase inhibitors), antihypertensive, anti-inflammatory, anticonvulsant, analgesic, antiprotozoal, anti-trichinellosis, antidiabetic, anti-HIV, antimicrobial, antitubercular, anticancer, antihistaminic, anti-oxidant, antiviral, antiparasitic agents, diuretic, and DNA binding activities [9, 10, 11, 12, 13, 14, 15, 16, 17, 18].

The current scenario knowledge of the drug development process was reviewed. The drug development process was challenging, expensive, and time-consuming. There are several methodologies that can be undertaken for lead discovery processes, such as screening process, drug metabolism studies, clinical observation

studies, natural product chemistry, and rational approaches to lead discovery. Quantitative correlation of molecules and the biological activity to find out with the help of quantitative structure-activity relationship (QSAR) modeling approach. The 2D-QSAR models are able to generate the equations by multiple linear regression and partial least squares regression analysis and assed the regression coefficient (r2), cross-validation (q2), and Fischer test (F-test) determination with the help of statistical parameters [19, 20, 21, 22, 23, 24].

The present work was to synthesize some novel substituted benzimidazole derivatives with their persistence and finding the correlation between physicochemical properties parameter and the antitubercular activity. This correlation will be essential to develop rational chemotherapeutic agents to delay the emergence of resistance and, ideally, shorten the duration of therapy of this infection.

MATERIALS AND METHODS: The chemicals of analytical grade required for the substituted some novel benzimidazole derivatives were purchased from Sigma-Aldrich and SD fine chemicals (India). Synthesized compounds were determined for their melting points with the help of precision melting point apparatus and were uncorrected. Completion of the reaction was confirmed by TLC on silica gel-G plates and the spots were visualized in the UV chamber or iodine chamber. IR spectra of intermediates and derivatives compound were recorded by using on KBr pellets on a Jasco FTIR-460 plus spectrophotometer and vibrational frequencies expressed in cm^{-1}. ^{1}HNMR spectra were recorded on BRUKER 400 MHz spectrometer in deuterated DMSO using tetramethylsilane (TMS) as internal standard and chemical; shifts were recorded as δ (parts per million).

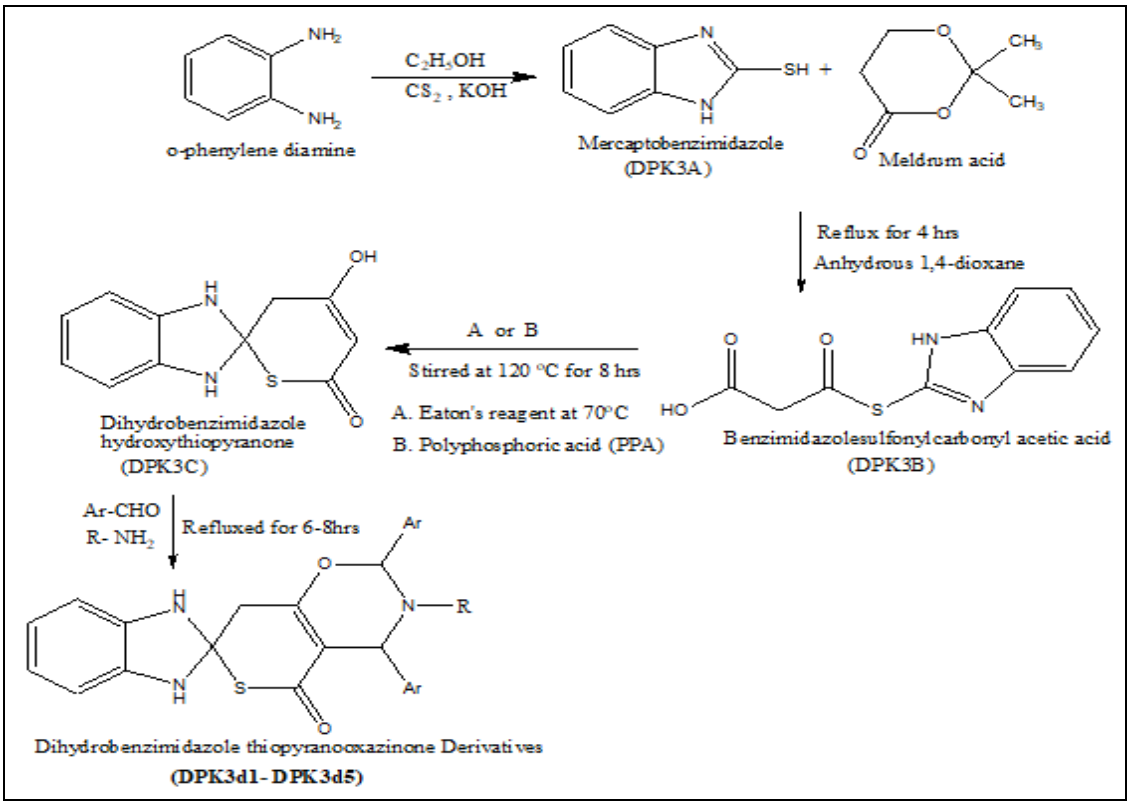

FIG. 1: SCHEME OF PREPARATION OF COMPOUNDS 3d1-DPK3d5

TABLE 1: SUBSTITUTION OF AROMATIC ALDEHYDE AND AMINE

Compound Code	Aromatic Aldehyde	Aromatic amine
DPK3d1	P-Chlorobenzaldehyde	Aniline
DPK3d2	P-Chlorobenzaldehyde	P-Nitroaniline
DPK3d3	Benzaldehyde	M-Nitroaniline
DPK3d4	Benzaldehyde	P-Nitroaniline
DPK3d5	Benzaldehyde	O-Nitroaniline

STEP 1: Synthesis of Mercaptobenzimidazole (DPK3A): O-phenylenediamine (10.8g, 0.1 moles) treated with carbon disulfide (7.67g, 0.1 moles) in the presence of potassium hydroxide (5.65g, 0.1 moles), 100 ml of 95% ethanol, and 15 ml of water used as a solvent; for 3 h condensed on a water bath. The solution mixture was filtered off after cooling. After that, 1-1.5g of activated charcoal was added carefully in the filtrate and refluxed on the water bath for 10 min; the filtration process helps to remove activated charcoal. The filtrate was treated with 100 ml of warm water at 60-70 ºC for 10 minutes. Dilute acetic acid was poured into the reaction mixture for acidification with gentle agitation to yield shiny crystals as a product, which is further kept in a refrigerator for three hours to allow the complete crystallization process. After the Buchner funnel helps to separate obtained reliable products, then the product at 40 ºC overnight; recrystallized from the ethanol.

STEP 2: Synthesis of Benzimidazolesulfonyl-Carbonyl Acetic Acid (DPK3B): Mercapto-benzimidazole (150 mg, 0.1 moles) was treated with Meldrum acid (184 mg, 0.1 moles) in the presence of anhydrous 1, 4- dioxane (5 ml, 0.1 moles) used as a solvent; for 4 hours condensed on a water bath. The solution mixture was filtered off after cooling. Then, the filtrate was introduced into a separatory funnel. The partition process is done through a saturated solution of sodium bicarbonate and ethyl acetate. From the partitioned solution, the mixture separates the aqueous layer and acidifies at pH 1-2 by adding carefully concentrated hydrochloric acid. Further made acidified solution several times extracted with methylene chloride. The obtained extracts dried and concentrate with the help of magnesium sulfate to assume targeted products and recrystallized from the benzene or hexane.

STEP 3: Synthesis of Dihydrobenzimidazole Hydroxythiopyranone (DPK3C): Benzimidazole-sulfonylcarbonyl acetic acid (98 mg, 0.1 moles) treated with polyphosphoric acid (1 g, 0.1 moles, 116%) in an Erlenmeyer flask was stirred at 120 ºC for 6-8 h. The solution mixture was filtered off after cooling and added 10 ml of water with vigorous stirring. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol.

STEP 4: General procedure for the synthesis of Dihydrobenzimidazole Thiopyranooxazinone Derivatives (DPK3d1-DPK3d5): Dihydrobenzimid-azole hydroxythiopyranone (1g, 0.1 moles) treated with an aromatic aldehyde (1.5g, 0.1 moles) in the presence of ethanol 10ml used as a solvent; for 6-8 hours condensed on a water bath. The solution mixture was filtered off after cooling. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the dimethylformamide or ethanol [25, 26, 27].

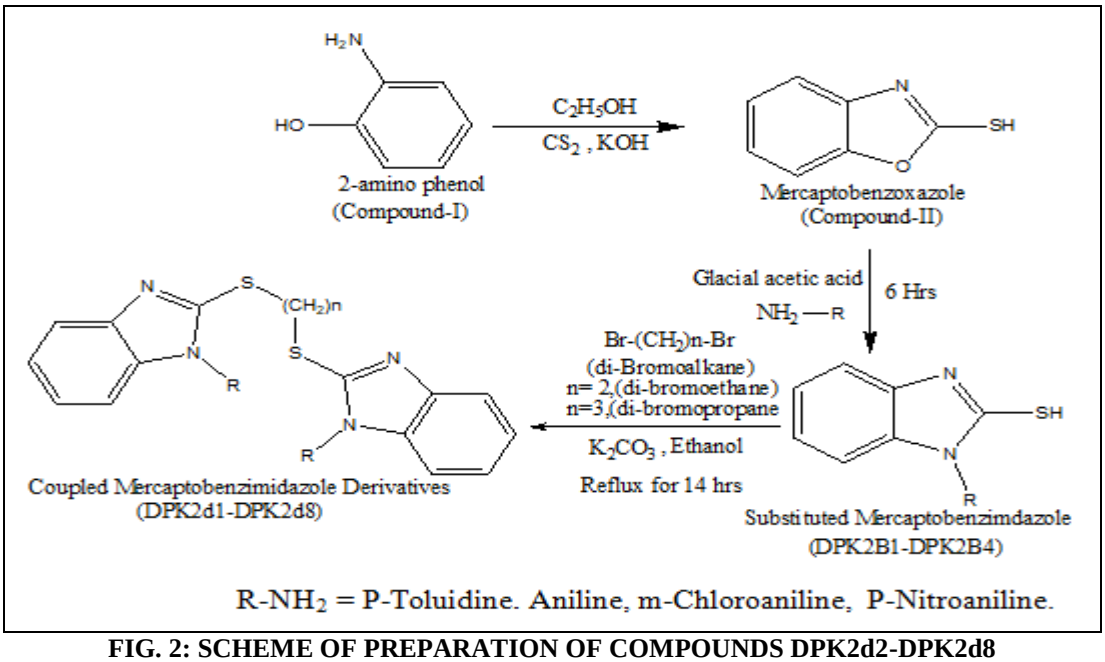

FIG. 2: SCHEME OF PREPARATION OF COMPOUNDS DPK2d2-DPK2d8

STEP 1: Synthesis of Mercaptobenzoxazole (DPK2A): 2-amino phenol (10.91g, 0.1 moles) treated with carbon disulfide (7.67g, 0.1 moles) in the presence of potassium hydroxide (5.65g, 0.1 moles), 100 ml of 95% ethanol and 15 ml of water used as the solvent; for 3 h condensed on a water bath. The solution mixture was filtered off after cooling. After that, 1-1.5g of activated charcoal was added carefully in the filtrate and refluxed on the water bath for 10 min; the filtration process helps to remove activated charcoal. The filtrate was treated with 100 ml of warm water at 60-70 ºC for 10 min. Dilute acetic acid was poured into the reaction mixture for acidification with gentle agitation to yield shiny crystals as a product, which is further kept in a refrigerator for three hours to allow the complete crystallization process. After the Buchner funnel helps to separate obtained solid products, then the product dried at 40 ºC overnight; recrystallized from the ethanol.

STEP 2: General Procedure for Synthesis of Substituted Mercaptobenzimidazole (DPK2B1-DPK2B4): Mercaptobenzoxazole (5.5g, 0.1 moles) was treated with primary aromatic amine (2.7g, 0.1 moles) and which was dissolved in 15 ml of glacial acetic acid. Then, the prepared solution mixture was condensed on a water bath for 6 h. The solution mixture was filtered off after cooling. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol.

STEP 3: General Procedure for Synthesis of Symmetrical Coupling Mercaptobenzimidazole Derivatives (DPK2d1-DPK2d8): Substituted Mercaptobenzimidazole (5g, 0.02 moles) (DPK2B1 -DPK2B4) was treated with (2.3g, 0.01 moles) with dibromoalkane (1, 2- dibromoethane or 1, 3-dibromopropane) which was dissolved in 60 ml of ethanol. Further (5g, 0.01 moles), anhydrous potassium carbonate is used as a deacidifying agent. Then, the prepared solution mixture was condensed on a water bath for 14 h. The solution mixture was filtered off after cooling. The neutralization did through an added prepared 2N aqueous solution of sodium hydroxide. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol [28, 29].

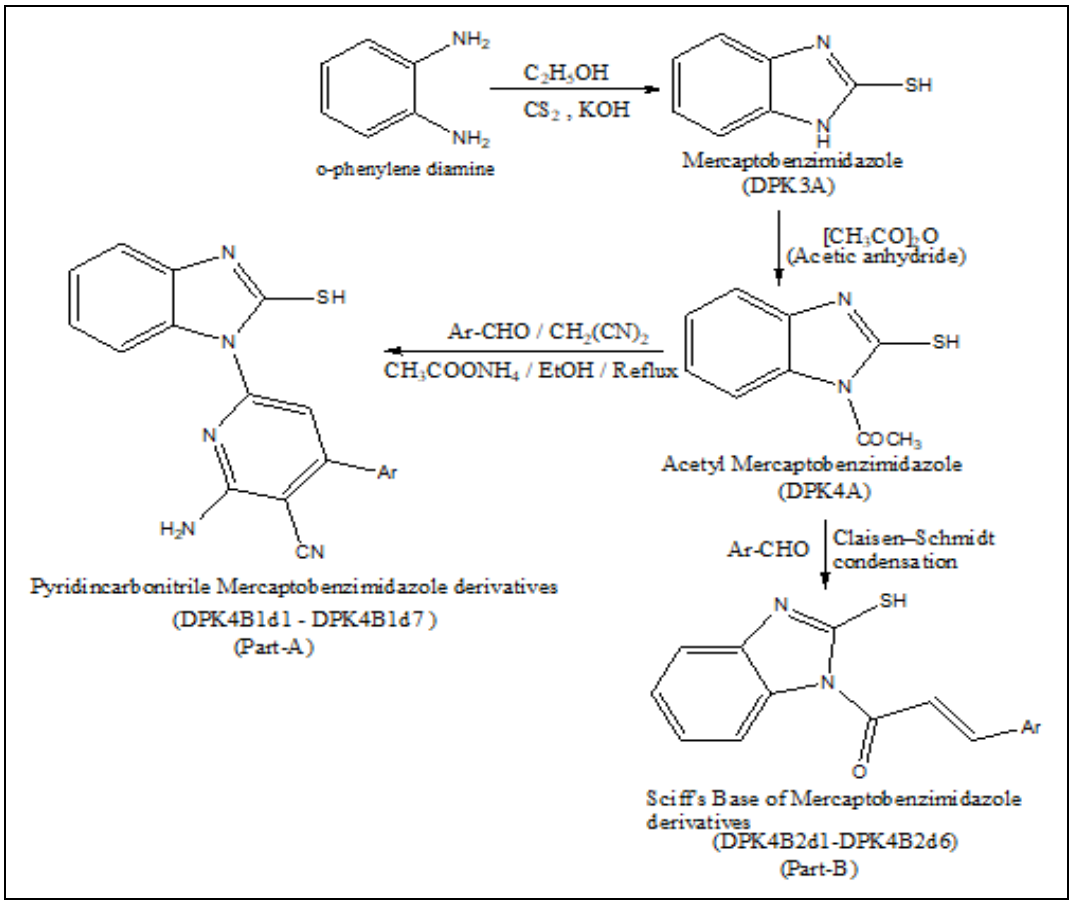

FIG. 3: SCHEME OF PREPARATION OF COMPOUNDS PART-A AND PART-B

TABLE 2: SUBSTITUTION OF AROMATIC ALDEHYDE

Compound Code	Ar-CHO	Compound Code	Ar-CHO
DPK4B1d1	Furfural aldehyde	DPK4B2d1	Furfural aldehyde
DPK4B1d2	Cinnamaldehyde	DPK4B2d2	P-Chlorobenzaldehyde
DPK4B1d3	O-Nitrobenzaldehyde	DPK4B2d3	O-Chlorobenzaldehyde
DPK4B1d4	P-Chlorobenzaldehyde	DPK4B2d4	O-Nitrobenzaldehyde
DPK4B1d5	Benzaldehyde	DPK4B2d5	Benzaldehyde
DPK4B1d6	2-Hydroxybenzaldehyde	DPK4B2d6	2-Hydroxybenzaldehyde
DPK4B1d7	O-Chlorobenzaldehyde		

STEP 1: Synthesis of Mercaptobenzimidazole (DPK3A): O-phenylenediamine (10.8g, 0.1 moles) treated with carbon disulfide (7.67g, 0.1 moles) in the presence of potassium hydroxide (5.65g, 0.1 moles), 100 ml of 95% ethanol, and 15 ml of water used as a solvent; for 3 h condensed on a water bath. The solution mixture was filtered off after cooling. After that, 1-1.5g of activated charcoal was added carefully in the filtrate and refluxed on the water bath for 10 min; the filtration process helps to remove activated charcoal. The filtrate was treated with 100 ml of warm water at 60-70 ºC for 10 min. Dilute acetic acid was poured into the reaction mixture for acidification with gentle agitation to yield shiny crystals as a product, which is further kept in a refrigerator for three hours to allow the complete crystallization process. After the Buchner funnel helps to separate obtained solid products, then the product dried at 40 ºC overnight; recrystallized from the ethanol.

STEP 2: Synthesis of N-Acetylmercapto-Benzimidazole (DPK4A): Mercaptobenzimidazole (5.5g, 0.1 moles) was treated with acetic anhydride (5ml, 0.1moles) in the presence of glacial acetic acid (5ml, 0.1moles) and 5ml of pyridine used as an acetylating agent. Prepared solution mixture refluxed on a sand bath for 10-15 min. The solution mixture was filtered off after cooling. Filtrate, pours it slowly in 100ml of ice-cold water and stirring with the help of a glass rod. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol.

STEP 3: Synthesis of Pyridincarbonitrile Mercaptobenzimidazole Derivatives (DPK4B1d1 DPK4B1d7): (Part-A): A series of N-Acetyl-mercaptobenzimidazole incorporating pyridine nucleus linked in the first position. Pyridin-carbonitrile mercaptobenzimidazole derivatives were prepared by direct one-pot reaction of N-Acetylmercaptobenzimidazole (2g, 0.1 moles) with the suitable aromatic aldehydes (1.5g, 0.1 moles) in the presence of malononitrile (5ml, 0.1 moles), ammonium acetate (2g, 0.1 moles) and 10ml of ethanol used as a solvent; for 4 hours condensed on a water bath. The solution mixture was filtered off after cooling. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol.

STEP 4: Synthesis of Mercaptobenzimidazole-Combined Chalcone Derivatives: (DPK4B2d1-DPK4B2d6): (Part-B): N-Acetylmercapto-benzimidazole (2g, 0.01moles) was treated with an aromatic aldehyde (1.5g, 0.01moles), 10 ml of 95% ethanol used as a solvent in an RBF equipped with a magnetic stirrer. After that, the prepared 10ml solution of 0.1N sodium hydroxide was added dropwise to the above reaction vessel with vigorous stirring at 20-25 ºC for 30 min. The neutralization did through an added prepared 0.1N hydrochloric acid. After the Buchner funnel helps to separate obtained solid products, then the product dried in the air and recrystallized from the ethanol [30, 31, 32, 33, 34].

Spectral Characterization Data of Substituted Benzimidazole Derivatives:

DPK3d1: FTIR (KBr, cm^{-1}): 3402, 3464 (N-H), 3109 (C-H, Ar), 1627 (C=O), 1450 (C=C, Ar), 1033 (C-N), 964 (C-O-C), 879 (C-Cl), 709 (C-S). ^{1}H NMR (δ ppm): 10.5 (bs, 1H, NH), 7.80 (s, 1H, CH), 7.10-7.60 (m, 3H, Ar-H), 2.50 (s, 1H, CH).

DPK3d2: FTIR (KBr, cm^{-1}): 3286, 3586 (N-H), 3039 (C-H, Ar), 1666 (C=O), 1442 (C=C, Ar), 1342, 1573 (NO_2, Ar), 1141 (C-N), 1087 (C-O-C), 779 (C-Cl), 686 (C-S). ^{1}H NMR (δ ppm): 12.50 (s, 1H, NH), 10.50 (s, 1H, NH), 7.90-8.00 (s, 1H, CH), 6.50-7.60 (m, 3H, Ar-H), 2.50 (s, 1H, CH).

DPK3d3: FTIR (KBr, cm^{-1}): 3171, 3232 (N-H), 3039 (C-H, Ar), 1666 (C=O), 1442 (C=C, Ar), 1180 (C-O-C), 1149 (C-N), 748 (Cl), 655 (C-S).

DPK3d4: FTIR (KBr, cm^{-1}): 3171, 3255 (N-H), 3093 (C-H, Ar), 1643 (C=O), 1442 (C=C, Ar), 1357, 1558 (NO_2, Ar), 1211(C-O-C), 1149 (C-N), 648 (C-S). ^{1}H NMR (δ ppm): 13.00 (s, 1H, NH), 10.00 (s, 1H, NH), 8.50 (s, 1H, CH), 6.50-8.20 (m, 3H, Ar-H), 2.50 (s, 1H, CH).

DPK3d5: FTIR (KBr, cm^{-1}): 3302, 3387 (N-H), 3047 (C-H, Ar), 1635 (C=O), 1481 (C=C, Ar), 1365, 1527 (NO_2, Ar), 1149 (C-O-C), 1087 (C-N), 601 (C-S). ^{1}H NMR (δ ppm): 13.00 (s, 1H, NH), 10.00 (s, 1H, NH), 8.00 (s, 1H, CH), 7.50-7.70 (m, 3H, Ar-H), 2.50 (s, 1H, CH).

DPK2d1: FTIR (KBr, cm^{-1}): 3063 (C-H, Ar), 2962 (C-H, Aliphatic), 1512 (C=C), 1265 (C-N), 609 (C-S). ^{1}H NMR (δ ppm): 7.071- 9.862 (m, 3H, Ar-H), 2.015-3.403 (m, 1H, CH).

DPK2d2: FTIR (KBr, cm^{-1}): 3070 (C-H, Ar), 2939 (C-H, Aliphatic), 1512 (C=C), 1265 (C-N), 609 (C-S). ^{1}H NMR (δ ppm): 7.073-9.841 (m, 3H, Ar-H), 2.335-3.382 (m, 1H, CH).

DPK2d3: FTIR (KBr, cm^{-1}):3063 (C-H, Ar), 2924 (C-H, Aliphatic), 1550 (C=C), 1265 (C-N), 756 (C-S). ^{1}H NMR (δ ppm): 7.004-9.993(m, 3H, Ar-H), 2.039-3.377 (m, 1H, CH).

DPK2d4: FTIR (KBr, cm^{-1}): 3063 (C-H, Ar), 2994 (C-H, Aliphatic), 1525 (C=C), 1265 (C-N), 756 (C-S). ^{1}H NMR (δ ppm): 7.005-9.941(m, 3H, Ar-H), 2.043-3.401 (m, 1H, CH).

DPK2d5: FTIR (KBr, cm^{-1}): 3124 (C-H, Ar), 2924 (C-H, Aliphatic), 1535 (C=C), 1280 (C-N), 871 (C-Cl), 756 (C-S). ^{1}H NMR (δ ppm): 7.005-9.941(m, 3H, Ar-H), 2.043-3.401 (m, 1H, CH).

DPK2d6: FTIR (KBr, cm^{-1}): 3070 (C-H, Ar), 2800 (C-H, Aliphatic), 1535 (C=C), 1280 (C-N), 793 (C-Cl), 702 (C-S). ^{1}H NMR (δ ppm): 7.075-10.138 (m, 3H, Ar-H), 2.064-3.394 (m, 1H, CH).

DPK2d7: FTIR (KBr, cm^{-1}): 3078 (C-H, Ar), 2893 (C-H, Aliphatic), 1597 (C=C), 1311 (NO_2), 1188 (C-N), 840 (C-S**). ^{1}H NMR (δ ppm):** 9.9941 (bs, 1H, NH), 6.589-7.825 (m, 3H, Ar-H), 2.123-3.362 (m, 1H, CH).

DPK2d8: FTIR (KBr, cm^{-1}): 3039 (C-H, Ar), 2939 (C-H, Aliphatic), 1651 (C=C), 1427 (NO_2), 1149 (C-N), 879 (C-S). ^{1}H NMR (δ ppm): 6.586-9.9841 (m, 3H, Ar-H), 2.498-3.347 (m, 1H, CH).

DPK4B1d1: FTIR (KBr, cm^{-1}): 3095 (Ar-CH), 2916 (CH Aliphatic), 2515(SH), 2322 (C≡N), 1519 (C=C), 1249 (C-N), 1018(C-O-C), 671 (C-S). ^{1}H NMR (δ ppm): 6.682-8.863 (m, Ar-H), 2.501-3.361 (s, SH).

DPK4B1d2: FTIR (KBr, cm^{-1}): 3185 (Ar-CH), 3047 (CH Aliphatic), 2385 (SH), (C≡N), 1597 (C=C), 1226 (C-N), 710 (C-S). ^{1}H NMR (δ ppm): 7.249-8.098 (m, Ar-H), 3.345-4.533 (s, SH), 2.500-2.525(d, Ethylene).

DPK4B1d3: FTIR (KBr, cm^{-1}): 3063 (Ar-CH), 2924 (CH Aliphatic), 2612 (SH), (C≡N), *1575* (C=C), 1483, 1350 (NO_2), 1250 (C-N), 752 (C-S). ^{1}H NMR (δ ppm): 6.680-8.306 (m, Ar-H), 2.434-3.41 (s, SH).

DPK4B1d4: FTIR (KBr, cm^{-1}): 3055 (Ar-CH), 2839 (CH Aliphatic), 2337 (SH), 2214 (C≡N), 1550 (C=C), 1250 (C-N), 825 (C-Cl), 752 (C-S). ^{1}H NMR (δ ppm): 6.752-7.951 (m, Ar-H), 2.445-3.356 (s, SH).

DPK4B1d5: FTIR (KBr, cm^{-1}): 3086 (Ar-CH), 2916 (CH Aliphatic), 2515 (SH), 2322 (C≡N), 1519 (C=C), 1249 (C-N), 671 (C-S). ^{1}H NMR (δ ppm): 7.463-7.950 (m, Ar-H), 2.499- 4.993 (s, SH).

DPK4B1d6: FTIR (KBr, cm^{-1}): 3641 (OH), 3302, 3194 (NH), 3047 (Ar-CH), 2931 (CH Aliphatic), 2337 (SH), (C≡N), 1527 (C=C), 1249 (C-N), 646 (C-S**). ^{1}H NMR (δ ppm):** 6.333-7.308 (m, Ar-H), 2.498-3.803 (s, SH).

DPK4B1d7: FTIR (KBr, cm^{-1}): 3047 (Ar-CH), 2939 (CH Aliphatic), 2337 (SH), (C≡N), 1545 (C=C), 1219 (C-N), 896 (C-Cl), 702 (C-S). ^{1}H NMR (δ ppm): 7.529-8.687 (m, Ar-H), 2.501-3.526 (s, SH).

DPK4B2d1: FTIR (KBr, cm^{-1}): 3047 (Ar-CH), 2908 (CH Aliphatic), 2337 (SH), 1666 (C=O), 1566 (C=C), 1257 (C-N), 1188 (C-O-C), 696 (C-S). ^{1}H NMR (δ ppm): 6.4-8.5 (m, Ar-H), 3.3- 6.3 (m, CH), 2.3-2.6 (s, SH).

DPK4B2d2: FTIR (KBr, cm^{-1}): 3147 (Ar-CH), 2965 (CH Aliphatic), 2299 (SH), 1689 (C=O), 1512 (C=C), 1319 (C-N), 709 (C-Cl), 696 (C-S). ^{1}H NMR (δ ppm): 7.114-10.016 (m, Ar-H), 3.386-4.492 (m, CH), 2.377-2.652 (s, SH).

DPK4B2d3: FTIR (KBr, cm^{-1}): Ar-CH), 2965 (CH Aliphatic), 2453 (SH), 1689 (C=O), 1627 (C=C), 1365 (C-N), 709 (C-Cl), 648 (C-S). ^{1}H NMR (δ ppm): 7.114-10.016 (m, Ar-H), 3.386-4.492 (m, CH), 2.377-2.652 (s, SH).

DPK4B2d4: FTIR (KBr, cm^{-1}): 3063 (Ar-CH), 2931 (CH Aliphatic), 2360 (SH), 1674 (C=O), 1625 (C=C), 1365 (C-N), 1565, 1442 (NO_2), 678 (C-S). ^{1}H NMR (δ ppm): 7.514-8.046 (m, Ar-H), 3.340-5.556 (m, CH), 2.503 (s, SH).

DPK4B2d5: FTIR (KBr, cm^{-1}): 3063 (Ar-CH), 2965 (CH Aliphatic), 2453 (SH), 1674 (C=O), 1620 (C=C), 1265 (C-N), 655 (C-S). ^{1}H NMR (δ ppm): 7.222-8.529 (m, Ar-H), 3.350-4.489 (m, CH), 2.360-2.641 (s, SH).

DPK4B2d6: FTIR (KBr, cm^{-1}): 3680 (OH), 3115 (Ar-CH), 2993 (CH Aliphatic), 2453 (SH), 1712 (C=C), 1645 (C=O), 1620 (C=C), 1357 (C-N), 655 (C-S). ^{1}H NMR (δ ppm): 7.108-8.018 (m, Ar-H), 3.012-3.386 (m, CH), 2.369-2.642 (s, SH).

2D-QSAR Study using Software Vlife Molecular Design Suite (Vlife MDS): 2D-QSAR models were performed with the help of two methods such as MLR and PLS. The calculating the molecular descriptors, after that by manual data selection method (Auto method using sphere exclusion method) were selected training and test sets. The variable selection method such as MLR and PLS were executed using the stepwise forward, backward method. The auto-scaling was applied with cross-correlation limit 1. The 15 molecules as a training set and 8 molecules as a test set were selected accordingly activity variation manually.

Calculations of Molecular Descriptors: The Vlife MDS 4.6 software was used to calculating of molecular descriptors. Molecular descriptors include physicochemical descriptors, alignment independent descriptors, and atom type count descriptors. In class of physicochemical descriptors include total 239 descriptors and based on physicochemical properties of the compounds, whereas alignment independent and atom type count include more than 700 and total of 99 descriptors, respectively. The MLR and PLS was carried out with help of Vlife software. After that, generate the equation of MLR and PLS according to the 3D structure of compounds by selecting the best suitable descriptors shown in **Table 3** [35, 36].

TABLE 3: SELECTING THE BEST SUITABLE DESCRIPTORS FOR 2D- QSAR STUDY

Name of descriptor	Category	Meaning
SsOHcount	Estate Number	In single bond to connected total number of –OH group.
Ipc Average	Information theory-based	Theory-based information descriptors.
Delta AlphaA	Topology	Molecular motion.
Delta AlphaB	Topology	Molecular connectivity
Ipc	Information theory Based	Theory-based information descriptors.
chi6chain	Chiv chain	Signifies atomic connectivity for a six-membered ring

RESULTS AND DISCUSSION: In this research study, we have reported twenty-six compounds were synthesized by various methodology. These compounds structurally elucidated by analytical studies such as determining physical constant and spectral studies such FTIR, ^{1}HNMR, showed satisfactory results. These newly synthesized analogues were screened against *in-vitro* antitubercular activity by using Microplate Alamar Blue Assay (MABA) method against *Mycobacterium tuberculosis* (H37Rv strain, ATCC 27294). Further, 2D-QSAR studies of some novel substituted benzimidazole derivatives were carried out on an Intel core 2 duo processor with Windows XP operating system by using Vlife MDS software version 4.6.

***In-vitro* Antitubercular Activity:** Synthesized novel substituted benzimidazole derivatives were screened by using Microplate Alamar Blue Assay (MABA) method against *Mycobacterium tuberculosis* for antitubercular activity testing.

Synthesized compounds having observed activity are shown in **Table 5**. Synthesized substituted benzimidazole compounds like DPK3d1, DPK2d1, DPK2d2, DPK2d3, DPK4B1d2, DPK4B2d1 and DPK4B2d2 had shown exhibited potent anti-tubercular activity, whereas remaining compounds shown moderate activity as compared to Pyrazinamide, Ciprofloxacin, and Streptomycin used as standard drugs.

2D-QSAR Analysis: From the results of 2D-QSAR studies can be seen that MLR and PLS method statistically significant model with respect to regression coefficient (r^2) and cross-validation (q^2).

In the MLR model, r^2 0.9344 and q^2 0.1813 are obtained. The generated MLR equation shown in table 4, there are four descriptors are involved such as SsOHcount, Ipc Average, Delta AlphaA, and Delta AlphaB. The MLR model executed all the descriptors are positively contributed to the antitubercular activity. The comparative of observed and predicted activity for the 2D-QSAR MLR method of antitubercular activity is shown in **Table 5**. The observed activity *vs*. predicated activity for the 2D-QSAR MLR method shown in **Fig. 4**. The contribution and fitness plot for the MLR model shown in **Fig. 6, 8** respectively.

In the PLS model, r^2 0.8320 and q^2 0.1626 are obtained. In the generated PLS equation shown in **Table 4**, three descriptors are involved: SsOH count, chi6chain, and Ipc. The PLS model executed all the descriptors are positively contributed to the antitubercular activity. The comparative of observed and predicted activity for 2D-QSAR PLS model of antitubercular activity shown in **Table 5**. The observed activity *vs*. predicated activity for the 2D-QSAR PLS model is shown in **Fig. 5**. The contribution and fitness plot for the PLS model shown in **Fig. 7, 9** respectively.

TABLE 4: 2D-QSAR EQUATION OF MLR AND PLS METHOD FOR *IN-VITRO* ANTITUBERCULAR ACTIVITY

Statistical Method	Equation	N	r^2	q^2	F test	r^2 se	q^2 se
MLR	SsOHcount 11.4293 (±1.2622) + IpcAverage0.0000(±0.0000) + Delta AlphaA 230.9890(±58.2261) + Delta AlphaB 107.0230(±40.4643) -0.1101	15	0.9344	0.1813	35.58	1.2051	4.2561
PLS	SsOHcount11.6575 + chi6chain 5.3685 + Ipc 0.0000 +0.2356	15	0.8320	0.1626	29.70	1.7601	3.9293

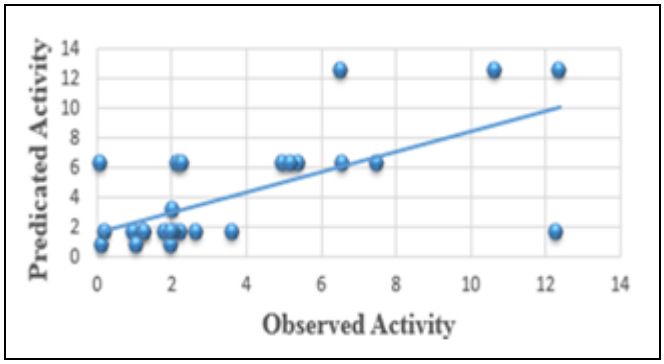

FIG. 4: OBSERVED ACTIVITY *vs*. PREDICATED ACTIVITY FOR 2D-QSAR MLR MODEL

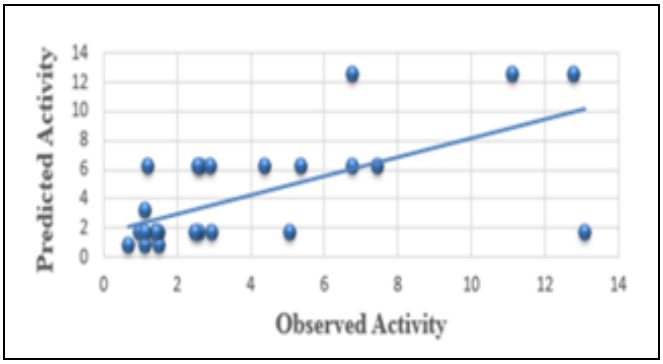

FIG. 5: OBSERVED ACTIVITY *vs*. PREDICATED ACTIVITY FOR 2D-QSAR MLR MODEL

TABLE 5: COMPARATIVE OF OBSERVED AND PREDICTED ACTIVITY FOR 2D-QSAR MODEL OF ANTITUBERCULAR ACTIVITY

Compound Code	Predicated Activity (MLR Model)	Predicated Activity (PLS Model)	Observed Activity	Compound Code	Predicated Activity (MLR Model)	Predicated Activity (PLS Model)	Observed Activity
DPK3d1	3.603681	5.090853	1.6	DPK4B1d1	0.962201	0.982811	1.6
DPK3d2	10.663034	11.147778	12.5	DPK4B1d2	0.111661	1.5339	0.8
DPK3d3	2.134333	4.380618	6.25	DPK4B1d3	1.826716	1.433484	1.6
DPK3d4	6.517284	6.769023	12.5	DPK4B1d4	1.280473	1.429879	1.6
DPK3d5	6.547014	6.794589	6.25	DPK4B1d5	0.214133	1.531079	1.6
DPK2d1	2.221395	2.6054	1.6	DPK4B1d6	12.287154	13.0874	1.6
DPK2d2	2.67055	2.971311	1.6	DPK4B1d7	1.280536	1.429914	1.6
DPK2d3	2.071737	2.4993	1.6	DPK4B2d1	1.067328	0.681216	0.8
DPK2d4	2.281831	2.670457	6.25	DPK4B2d2	1.969209	1.132279	0.8
DPK2d5	4.965226	2.58256	6.25	DPK4B2d3	1.969216	1.132282	1.6
DPK2d6	5.397012	2.934322	6.25	DPK4B2d4	2.031271	1.132552	3.12
DPK2d7	5.190799	5.368429	6.25	DPK4B2d5	0.10422	1.22885	6.25
DPK2d8	7.509939	7.467682	6.25	DPK4B2d6	12.389889	12.789768	12.5

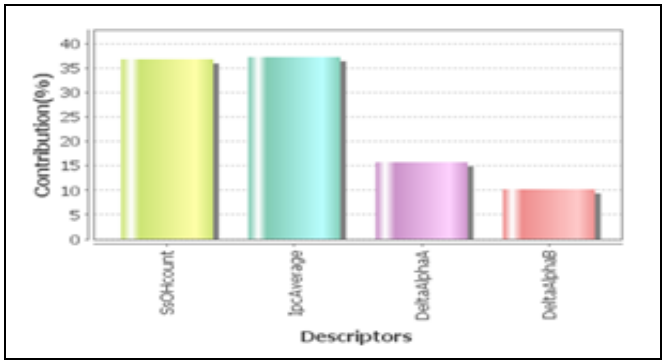

FIG. 6: CONTRIBUTION PLOT FOR TRAINING SET FOR MLR MODEL

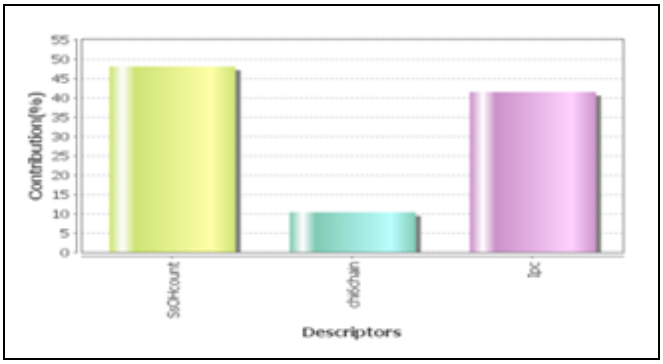

FIG. 8: CONTRIBUTION PLOT FOR TRAINING SET FOR PLS MODEL

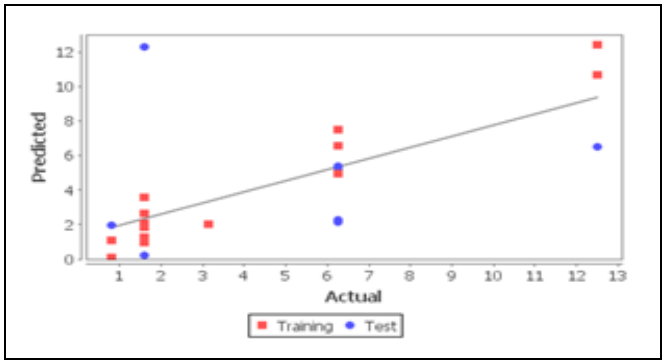

FIG. 7: FITNESS PLOT FOR TRAINING SET FOR ACTUAL VALUE (X-AXIS) *vs.* PREDICTED VALUE (Y-AXIS) FOR MLR MODEL

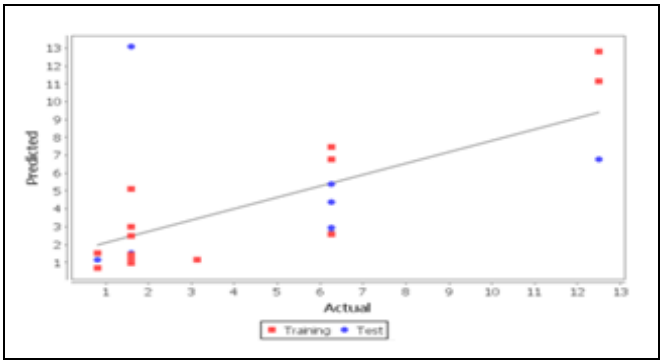

FIG. 9: FITNESS PLOT FOR TRAINING SET FOR ACTUAL VALUE (X-AXIS) *vs.* PREDICTED VALUE (Y-AXIS) FOR PLS MODEL

CONCLUSION: A series of novel substituted benzimidazole derivatives were derivatives were efficiently synthesized and screened for their *in-vitro* antitubercular activity with their 2D-QSAR studies. The antitubercular activity results confirmed that compounds DPK3d1, DPK2d1, DPK2d2, DPK2d3, DPK4B1d2, DPK4B2d1 and DPK4B2d2 have shown exhibited potent antitubercular activity as compared with standard drugs. 2D-QSAR methods such as MLR and PLS method studies shown that all the descriptors are directly proportional to the antitubercular activity.

The prediction activity in the test set fruitful for the development antitubercular activity.

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